

AD _____

Award Number: DAMD17-99-2-9001

TITLE: Center for the Integration of Medicine and Innovative Technology

PRINCIPAL INVESTIGATOR: John A. Parrish, M.D.

CONTRACTING ORGANIZATION: The General Hospital Corporation
Boston, Massachusetts 02114

REPORT DATE: November 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are
those of the author(s) and should not be construed as an official
Department of the Army position, policy or decision unless so
designated by other documentation.

20030130 199

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE November 2002	3. REPORT TYPE AND DATES COVERED Annual (15 Oct 01 - 15 Oct 02)
4. TITLE AND SUBTITLE Center for the Integration of Medicine and Innovative Technology		5. FUNDING NUMBERS DAMD17-99-2-9001
6. AUTHOR(S) : John A. Parrish, M.D.		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The General Hospital Corporation Boston, Massachusetts 02114 Email: jparrish@cbrc.mgh.harvard.edu		8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSORING / MONITORING AGENCY REPORT NUMBER
11. SUPPLEMENTARY NOTES		
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited		12b. DISTRIBUTION CODE
13. ABSTRACT (Maximum 200 Words) none provided		
14. SUBJECT TERMS endovascular devices, minimally invasive surgery, image guided therapy, tissue engineering		15. NUMBER OF PAGES 75
		16. PRICE CODE
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified
		20. LIMITATION OF ABSTRACT Unlimited

Table of Contents

Cover.....	1
SF 298.....	2
Table of Contents.....	3
Introduction.....	4
Body.....	12
Key Research Accomplishments.....	
Reportable Outcomes.....	58
Conclusions.....	
References.....	62
Appendices.....	65

**CENTER FOR INTEGRATION OF MEDICINE AND INNOVATIVE TECHNOLOGY
Annual Progress Report****1.0 INTRODUCTION**

The Center for Integration of Medicine and Innovative Technology (CIMIT) has completed the fiscal year 10/1/01 through 9/30/02 under Cooperative Agreement Number DAMD17-99-2-9001. CIMIT is a non-profit consortium of world-leading academic and research institutions founded by Partners HealthCare System, Massachusetts General Hospital, Brigham and Women's Hospital, Massachusetts Institute of Technology, and Charles Stark Draper Laboratory. The overall goal of the program has evolved beyond minimally invasive therapy to include other aspects of acute care using high technology approaches.

CIMIT's mission is to improve patient care by bringing together scientists, engineers, and clinicians to catalyze development of innovative technology, emphasizing minimally invasive diagnosis and therapy.

1.1 Key Accomplishments by Program – Project – Principal Investigator**Endovascular Devices – Cardiomyocyte Repopulation – Steven Oesterle, MD, MGH**

The major accomplishment for the Cardiomyocyte Repopulation project was the first feasibility testing of a novel, catheter-based method for autologous bone marrow stem cell transplantation to heart muscle. This completes this project.

Minimally Invasive Surgery – Endoscopic Anastomosis – David Torchiana, MD, MGH

Chronic studies in a large animal model demonstrated that FocalSeal surgical sealant is an effective hemostatic adjunct without associated tissue toxicity when applied to blood vessel anastomoses sites. This completes this project.

Minimally Invasive Surgery - Craniofacial Surgery Planning – Leonard Kaban, MD, MGH

The CIMIT team has developed a user interface for six degree-of-freedom manipulation of 3-D graphical objects using a standard computer mouse. Also, an upgraded version of a 3-D axis manipulation tool was implemented in the current version of the 3-D Slicer. This completes this project.

Minimally Invasive Surgery - Robot-Assisted Surgery – Robert Howe, PhD, HMS

The CIMIT team is implementing a new approach that uses an electromagnetic tracker attached directly to the tip of the instrument. Based on this more accurate sensor, the team has developed a navigational aid that shows the location of the instrument tip relative to the internal mammary artery.

Image Guided Therapy - Focused Ultrasound for Cancer Tx – Ferenc Jolesz, MD, BWH

Several phased array systems were tested and results used to develop the final 208-channel phased array system in collaboration with a commercial manufacturer. This system was tested in rabbits. The results are good, demonstrating the ability of the system to coagulate tumor tissue similar in size and location to breast cancer. This completes this project.

Image Guided Therapy - Automated Image Segmentation – Carl-Fredrik Westin, PhD, BWH

The CIMIT team has introduced a new image feature, based on local phase, which describes local edge symmetry independent of absolute gray value. The phase is a natural bi-product from the filters used in the adaptive filtering scheme presented. Because phase is amplitude invariant, the measurements are robust with respect to smooth variations, such as bias field inhomogeneities present in all MR images. In order to enable validation of the phase-wire segmentation software, a system has been created that continuously records user interaction and automatically generates a database containing the number of user interactions, such as mouse events, and time stamps from various editing modules. This completes this project.

Tissue Engineering - Degradable Conductive Polymers – Robert Langer, ScD, MIT

The CIMIT team proposed a novel approach to the creation of bioerodible polypyrrole (Ppy). In this novel paradigm the rate of erosion of Ppy is controlled by the hydrolysis and ionization of pendant groups followed by the solubilization of Ppy oligomers. The team has verified the hypothesis that solubilization of Ppy solid and thin film substrates, via ionizable side chain moieties, can occur under physiological conditions. This completes this project.

Tissue Engineering - Polymer-Based Gene Delivery Platforms – Robert Langer, ScD, MIT

The CIMIT team has continued development on the first accelerated discovery approach for finding synthetic transfection vectors. This year the team has begun the synthesis of a library containing up to 3,500 individual polymers. In the near future, this library will be screened for gene transfer efficiency. Work has also been done to further characterize the polymers in the original poly(β -amino ester) library. The library was characterized along the following dimensions: (1) effective diameter of polymer-DNA complexes, (2) zeta potential of polymer-DNA complexes, and (3) relative uptake of complexes by 3T3 cells. This completes this project.

Tissue Engineering - Trans-Dermal Drug Delivery – James Weaver, PhD, MIT

A new approach to computer simulation of spatially complex systems was identified. The CIMIT team has obtained very encouraging results for a simulation of the transport of potent agents through the skin due to exposure of a small amount of the compound to the surface of the skin. This completes this project.

Tissue Engineering - Synthesis of Vascularized Living Systems – Joseph Vacanti, MD, MGH

Significant milestones in both fabrication and testing of microfabricated vascular scaffolds have been reached during this project. Polymer fabrication in both biocompatible and biodegradable matrices is moving ahead swiftly. Molds produced from PolyDiMethylSiloxane (PDMS), a biocompatible polymer, have been produced in both two- and three-dimensions. Three-dimensional vascular beds have been connected in parallel and run through initial fluid dynamic qualification studies. Bonded layers of biodegradable PLGA molded films have also been produced, a major milestone. This completes this project.

Tissue Engineering - Structures to Enable Vascularization – Jeffrey Borenstein, PhD, Draper

Major milestones in the design of scaffolds for endothelial cell seeding have been achieved. Several generations of networks have been produced, each representing a significant advance over previous designs. The first design with fully uniform flow, TEP-2, was generated on the wafer level and utilized to produce large numbers of silicon and polymer scaffolds for cell seeding. Design efforts were then transitioned to the modular networks TESTNET0 and

TESTNET1, which are more suited to fluid dynamic experiments and biocompatibility studies. In a major advance, a new technique for generating mask layouts has been developed in which computational techniques are used to automatically produce vascular networks with desired flow characteristics. This new layout tool has been applied to the generation of photomasks for vascular designs, thereby reducing the cost of photomasks from \$700 to \$15 and the layout time required from 2 weeks to 1 day. This completes this project.

Tissue Engineering - Minimally Invasive Meniscal Repair – Thomas Gill, MD, MGH

This research has demonstrated that a cell-based therapeutic approach can be used in the articular environment in a large animal model of meniscal tears. Further investigation during the second year sought to define the best delivery material and the best pre-seeding conditions of the reparative cells onto candidate scaffolds. A clinically applicable approach combining this technique with arthroscopic surgery might be developed based on these studies. This completes this project.

Tissue Engineering – Treatments for Ovarian Cancer – David MacLaughlin, PhD, MGH

In these studies, resorbable polyglycolic acid biopolymer matrices impregnated with cells transfected with the MIS gene were successfully implanted in over 80 immuno-compromised mice and bioactive MIS produced and absorbed by the blood stream. The effect of different sized biopolymer implants on the resulting serum MIS concentrations was also determined. This completes this project.

Tissue Engineering - MSCs for Tissue Engineering – Scott Adzick, MD, UPENN

The CIMIT team has made significant progress toward the clinical utilization of mesenchymal stem cells. Due to progress from other investigators in the field, it is clear that a mesenchymal stem cell of small phenotype, rather than the large fibroblastic phenotype used in our previous studies, has significantly greater differentiative capacity *in vitro*, and contains a higher frequency of Colony Forming Units-f forming cells. This completes this project.

New Initiatives - Outcome Assessment in Menorrhagia – Johanna Bosch, PhD, MGH

The CIMIT team has developed a self-administered questionnaire including the Health Utilities Index and EuroQol-5D to collect quality-of-life data in patients with menorrhagia. Upon the patient survey and its data analyses, the binary-gamble method will be used to assess community preferences for menorrhagia in a sample of the general population. The CIMIT team is awaiting final DoD approval for this project.

Simulation – Procedural Simulation – Steven Dawson, MD, MGH

The CIMIT team continued to see strong interest in the VIRGIL® system from emergency physicians, paramedics, and business people who have visited the CIMIT facility. The team has invested considerable time in redesigning the system so that it can be more easily transportable. New design considerations for the beta version of VIRGIL® include significant modifications to the instrument tracking system, a key component of the augmented reality tracking system, new containment methods for the hemothorax blood flow scenario, and new cooling and ventilation methods. This completes this project.

Trauma and Critical Care – Microsensors – Christopher Dube, PhD, Draper

Among the key results from this year is the repeatable detection of the microbial pathogen *E. coli* O157:H7 using individually functionalized μCANARY elements. In the previous quarter the team demonstrated detection of *E. coli* O157:H7 using commercially available antibodies. This completes this project.

Trauma and Critical Care – Hematoma Detection – Geoffrey Ling, MD, PhD, USUHS

The team has successfully completed a study of the RAFTS as it is applied to diagnosis of intracranial hematomas, pneumothorax and compartment syndrome. The results from this work demonstrate that the RAFTS can differentiate hematomas from brain and skull. Subsequently, the team reported the completed *in vivo* study that was performed in live anesthetized pigs. These studies show that the RAFTS can accurately detect the presence of hematomas at epidural, intraventricular, subdural and intraparenchymal sites in a clinically relevant model. Also in pigs, RAFTS can also detect as little as a 10% pneumothorax and as little as 2cc of either blood or saline in the muscle compartment. This completes this project.

Vulnerable Plaque – VP Detection and Treatment – James E. Muller, MD, MGH

Vulnerable Plaque Program continued to meet its goals and establish new ones. The main activity of the Program continues to be the scientific projects focusing on methods of detection and treatment of vulnerable plaque. Leadership of the Program continues to address thematic, administrative and support issues in an attempt to enhance the overall quality and scope of the Program. This completes this project.

Vulnerable Plaque – OCT for Vulnerable Plaque Detection – Brett Bouma, PhD, MGH

The CIMIT team has advanced the capabilities of OCT for imaging *in vivo* by resolving three key technical issues. First, the team has developed methods for displacing blood from the iliac and aorta using balloon occlusion and saline flush. Second, the team has demonstrated a sufficient image acquisition rate to avoid motion artifact due to respiration and pulsatile blood flow. Finally, the team has demonstrated that characteristic features in plaques can be resolved using a catheter that provides a resolution of approximately 10 microns. This completes this project.

Stroke - Optical Monitoring of Stroke – David Boas, PhD, MGH

Significant progress was made in diffuse optical technology for characterizing layered media. This technology is central to cerebral oximetry in which the layered structure of scalp, skull and brain must be characterized. The key developments include: 1) New time resolve near infrared spectroscopy instrumentation for improved optical property determination, 2) time resolved Monte-Carlo modeling of layered media and 3) composing and submitting a Human protocol for cerebral oximetry measurements on healthy people. This completes this project.

Stroke - Functional MRI in Cerebral Amyloid Angiopathy – Steven Greenberg, MD, MGH

Thus far, 4 control subjects and one CAA subject have been studied using fMRI. Data analysis revealed a robust response in blood flow to both visual stimulation and CO₂ inhalation in the control subjects, and analysis is still pending for our first CAA subject.

Technology Assessment - Inpatient Costs in Stroke – G. Scott Gazelle, MD, PhD, MGH

The Technology Assessment and Outcomes Analysis Program has evolved over three years with the support and guidance of CIMIT leadership. In view of changes in CIMIT over the years, the Program has been reshaped to concentrate our research efforts in two major focus areas: Vulnerable Plaque and the Operating Room of the Future. Also, service, policy and administrative components of the Program are now concentrated in a Program Core. This completes this project.

Core Programs – Regulatory Affairs – John Smith, MD, JD, MGH

The CIMIT Regulatory Affairs Program continues to assist FDA in implementing the “least burdensome means” concept as required by the Food and Drug Administration Modernization Act of 1997 (FDAMA). The Regulatory Affairs Program also continues to function as a point of access to FDA’s Center for Device and Radiological Health, providing information and academic resources to FDA managers and line reviewers. During this year, details on a presentation of CIMIT’s vulnerable plaque work were finalized with the agency. This completes this project.

1.2 Highlight Project

Synthesize Vascularized Living Systems from the Platform of Two-Dimensional Silicon Microfabrication Technologies and Adapt to Three-Dimensional Living Devices

Principal Investigator: Joseph Vacanti, MD, MGH

The overall goal of this project is to develop tissue-engineered devices composed of living cells on matrices which, upon implantation, are vascularized either *in vitro* or *in vivo*. The major project related to this goal is to synthesize vascularized systems from the platform of 2-D silicon microfabrication technologies and adapt to three-dimensional living devices.

One Specific Aim of this work is to design two-dimensional (2-D) and three-dimensional (3-D) microvascular network templates for the microfabrication of tissue-engineered organs. The ultimate goal is to culture endothelial cells in these microvascular networks, integrate them with layers of engineered tissues, and finally stack/fold/roll them to create 3-D conformations of living vascularized organs for implantation. The geometrical structure and topology of these microcirculatory networks must optimally provide physiological distributions of blood across the tissue bed, while providing maximal mass transfer of oxygen and nutrients to the surrounding tissue. Detailed quantitative analysis of hemodynamics and mass transport (of oxygen and nutrients) in complex microvascular networks is hence required in order to ensure all cells enjoy the sustained continuous supply of rich blood.

Key Results: Over the past year, the CIMIT team continued to develop and extend our infrastructure algorithms for design, modeling, and optimization of the microvascular networks. The tasks carried out in the past year can be summarized as:

- Development and implementation of strategies for the design of microvascular networks in 3-D,
- Further development of our computational model for simulation of blood flow microcirculatory networks, and its extension to 3-D networks, and

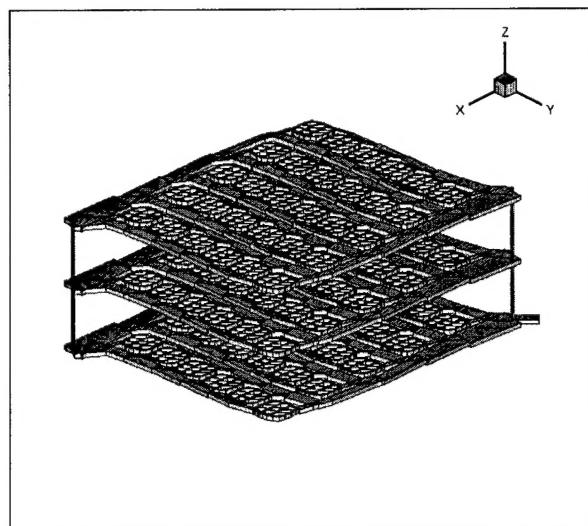
- Further development of our computational algorithm for simulation of mass transport of oxygen and nutrients in the intra- and extra-vascular regions across the tissue bed.

Specific Aim 1: Design and fabricate silicon and Pyrex based systems providing an array of etched channels to act as a mold for generating a living network in two dimensions. To accomplish this Specific Aim the following items will be addressed:

- Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold,
- Design bioreactors to house the device during tissue formation and folding,
- Develop assays to study the generation of tissue and its histological, biomechanical, and biochemical parameters,
- Investigate mechanisms of tissue development using molecular markers for gene developmental programs and programs of wound healing and regeneration, and
- Begin animal implantation studies to begin to understand perfusion, survival, and function of the living device.

Progress: After completing the detailed quantitative studies of our 2-D microvascular templates, we have moved towards extending the designs to 3-D. Due to the current limitations in microfabrication technologies, we are bound to use 2-D templates as building blocks of the 3-D design. Within such constraints, several strategies for three-dimensionalization are being developed, namely 'stacking', 'folding', and 'rolling'. The protocol for the *stacking* strategy has been already completed. In this strategy, the 2-D layers are connected using vertical through-holes called 'vias'. Figure 1 shows a typical 3-D network which has been designed based on our new two-dimensional design providing even distribution of blood flow rate on each 2-D layer. The size, location, and number of vias is flexible and can be chosen to optimize the 3-D design, based on the geometry and topology of the microvascular networks on the 2-D layers.

Fig. 1: A typical 3-D microvascular network developed based on the 'stacking' strategy. The 2-D layers used 'building blocks' in this design are based on our new 2-D networks that provide even distribution of blood flow rate on each layer.



as
on

Plan: The stacking strategy for 3-D networks will be perfected based on various designs for 2-D templates by optimizing the configuration of the 'vias', namely their location, size, and number. The 'folding' and 'rolling' strategies will be extensively examined and their potential for rapid prototyping of the networks in biodegradable polymers will be explored.

Specific Aim 2: Further development of our computational model for simulation of microfluidic networks: Extension to 3-D.

Progress: Our computational algorithm for simulation of blood flow in the microvascular networks was further developed and extended to 3-D. This algorithm takes into account the non-newtonian blood rheology and its particulate nature, both of which are important in modeling the microcirculation. The nonlinear dynamics of blood/cell flow is solved using a two-step algorithm devised and implemented as part of this work. In the past year, the extension of this algorithm to 3-D was devised and implemented using C computer programming language. The 3-D algorithm allows for detailed quantitative study of distribution of blood flow and hematocrit in the 3-D designs described in Specific Aim 1.

As an example, Figure 2 shows the distribution of flow rate in a typical 3-D microvascular network built based on 'stacking' strategy. The flow enters the network and keeps feeding the repeating capillary beds. As evident in the figure, the capillary beds receive an equal amount of blood flow. Further, each individual layer enjoys an adequate level of flow rate.

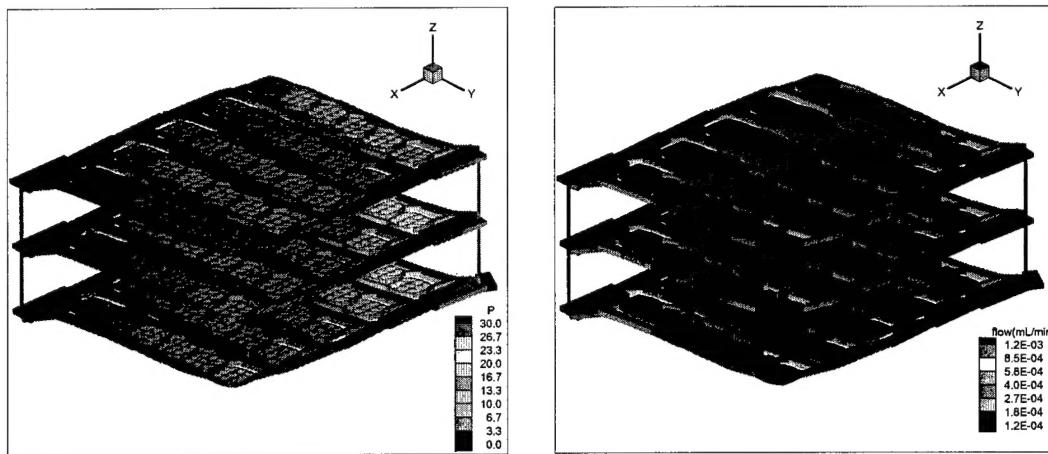


Fig. 2: Distribution of blood pressure (left panel) and flow rate (right panel) in a typical 3-D microvascular network.

In order to better demonstrate the distribution of blood's pressure and flow rate, Figure 3 focuses on one of the layers. As seen in this figure, blood's pressure gradually decreases from the arterial to venous side of the network. The capillary beds receive uniform distributions of flow rate.

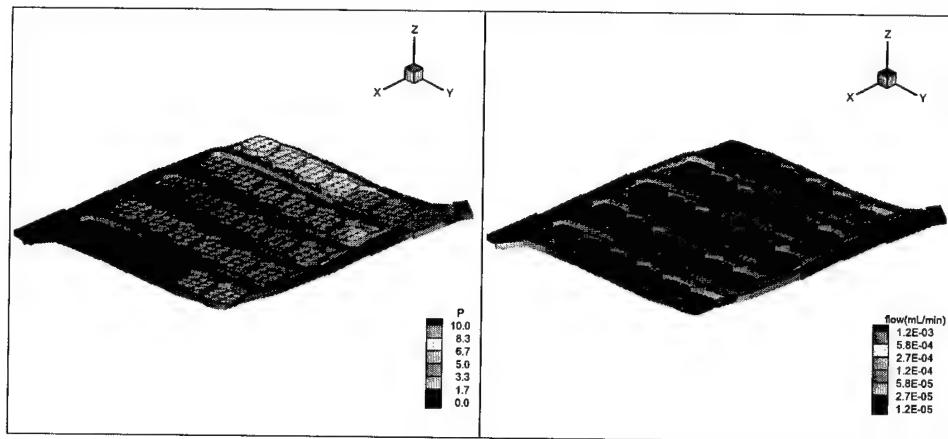


Fig. 3: Distribution of blood's pressure (left panel) and flow rate (right panel) in one of the layers of the 3-D design.

The 3-D algorithm provides a robust tool for examining different topological configurations of the vias in relation with the various designs of the individual layers and their impact on the distribution of hemodynamic state within a tissue bed.

Plan: In order to further validate our 2-D and 3-D computational algorithm, quantitative measurement of pressure loss, flow rate, and hematocrit will be performed in endothelialized microvascular systems, and the experimental results will be compared with the corresponding parameters calculated using the computational algorithm.

The 3-D algorithm will be used to assess details of different configurations of the stacking design, as discussed in Specific Aim 1. Further, it will be employed to evaluate other design strategies, namely 'folding', and 'rolling'.

2.0 ENABLING TECHNOLOGIES

2.1 ENDOVASCULAR DEVICES

Task 1: Cardiomyocyte Repopulation using Percutaneous Delivery of Tissue Engineered Systems

Principal Investigator: Stephen Oesterle, MD and Craig Thompson, MD, MGH, Boston, MA

Over 1.5 million adults experience acute myocardial infarction each year. More than 500,000 die from the event. Many others survive with significant impairment of left ventricular function. A multitude of diseases unrelated to Atherosclerosis can also result in varying degrees of heart failure, including sustained hypertension, viral myocarditis, and valvular insufficiency frequently lead to intractable ventricular dysfunction. Congestive heart failure (CHF) is amongst the most frequent diagnoses for patients admitted to acute care hospitals. CHF is associated with the longest lengths of stay for any of the cardiac Diagnostic Related Groups (DRGs). Acute and chronic care of patients with heart failure consumes billions of health care dollars. Beyond diuretics and other pharmaceutical preparations that "unload" failing hearts, there are few effective treatments for advanced heart failure. Adult mammalian myocardial cells are generally believed to be terminally differentiated with little or no capacity for repair or proliferation. Unlike skeletal muscle, irreversible injury to myocardial tissue predictably leads to akinesis, fibrosis and thinning.

The purpose of this project is to develop a tissue engineered device to replace myocardial muscle damaged by ischemia or inflammation and to develop a percutaneous catheter system for delivery to the heart using an *in vivo* porcine model.

Key Results: The major accomplishment for the Cardiomyocyte Repopulation project was the first feasibility testing of a novel, catheter-based method for autologous bone marrow stem cell transplantation to heart muscle. This completes this project. It should be noted that as of December 1, 2001, Dr. Stephen Oesterle assumed the position of Vice President of Medtronic, and has there for left Massachusetts General Hospital and CIMIT. Dr. Donald Baim has assumed the role of Acting Program Leader for the Endovascular Devices Program.

Specific Aim 1: To refine percutaneous catheter devices to achieve quantitative myocardial cell transfer.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 2: To develop a tissue engineered system of cardiomyocytes in hydro gel polymer for delivery into both healthy and damaged ventricles.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September

30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 3: To evaluate applicability of adult and fetal cardiomyocytes and stem cells as catheter-delivered donors. To devise proper mixtures of hydro gel polymers, and growth factors to support cardiac cells for catheter delivery.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

2.2 MINIMALLY INVASIVE SURGERY

Task 1: Minimally Invasive Cardiac Surgery – Endoscopic Coronary Anastomosis

Principal Investigator: David Torchiana, MD and Jennifer White, MD, MGH

This project entails laboratory development of a robotic interface in cardiac surgery to ensure safe and effective clinical application of the technology. Since the project's initiation in 1999, endoscopic coronary artery bypass ("E-CABG") using the robotic interface ("Zeus", Computer Motion, Inc.) has been performed in sixty-eight laboratory animals. Advancements have been made in the anatomical positioning of instrument ports, internal mammary artery harvesting, and surgical skill in performing a non-beating heart anastomosis using the robotic interface. An upgraded Zeus robotic interface acquired in December 2000 reduced surgical case interruption due to computer errors. Novel instruments including a proximal anastomotic device ("Symmetry", St. Jude Medical, Inc.) and surgical clips ("U-Clip", Coalescent Surgical, Inc.) have been integrated into the procedure.

In the course of this work, it has been appreciated that endoscopic robot-assisted dissection of the internal mammary artery is time consuming and difficult. In humans the vessel tends to course deep in the transversus thoracic muscle and out of the thorascopic view of the surgeon. In an attempt to overcome this problem, manipulation of the robotic interface through CT-image guidance has been developed to assist in the video-endoscopic dissection of the internal mammary artery. Professor Howe's group from Harvard's Department of Engineering has undertaken a joint effort with our laboratory to augment the internal mammary artery (IMA) takedown procedure using computer-assisted computerized tomography (CT) guidance with 3-dimensional surgical instrument registration. The procedure could lead to safer clinical left internal mammary artery (LIMA) dissection, since the intra-operative movement of the robotic interface would be linked directly to the anatomical course of the vessel as "mapped out" by the patient's pre-operative CT scan. In addition, it is expected that successfully linking data obtained from these pre-operative images to the procedure will enable instrument port placement to be optimized for each individual. This new emphasis on pre-operative image guidance should reduce instrument mechanical conflicts and increase the freedom of the instrument's movements to perform the task at hand.

Key Results: The MGH is one of two clinical sites in what will eventually be a five center clinical trial of IMA takedown with plans to enroll 250 patients in all. The institutional and DoD human use approval process is underway for this project. Dr. Torchiana is the Principal Investigator for this trial.

Specific Aim 1: Characterization of FocalSeal surgical sealant as a hemostatic adjunct.

Progress: Project completed. See Quarterly Progress Report for the period January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report for the period January 1, 2001 through March 31, 2001.

Specific Aim 2: Perform acute and chronic evaluation of a new micro-anastomotic device on coronary arteries.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Minimally-Invasive Cardiac Surgery under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 3: Development of a method for video-endoscopic coronary anastomosis.

This Specific Aim is to develop the closed chest E-CABG procedure in the laboratory during the pre-clinical investigation and move into the clinical setting in a four-step process. Laboratory studies directed towards device development and training of the surgical team will continue throughout all four phases. The clinical application will progress over a two-year period with phases of increasing surgical complexity and technical difficulty. Laboratory studies directed towards device development and training of the surgical team will continue throughout all phases.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Minimally-Invasive Cardiac Surgery under Cooperative Agreement No. DAMD17-02-2-0006.

Task 2: Endothelial Activation Markers as Molecular Targets for Innovative, Minimally Invasive Diagnosis and Therapy in Cardiovascular Disease

Principal Investigator: *Michael Gimbrone, MD, Brigham and Women's Hospital, (BWH), Boston, MA*

The endothelial cells (EC) that comprise the lining of the cardiovascular system constitute a dynamically mutable interface in health and disease. In response to various inflammatory, thrombotic and atherogenic pathophysiologic stimuli (e.g., cytokines, coagulation factors, bacterial and tumor products, advanced glycation endproducts, oxidized lipoprotein components, injurious agents, biomechanical stresses), EC can undergo phenotypic modulation to a dysfunctional state that is marked by expression of "activation antigens", such as E-selectin (ELAM-1) and VCAM-1 (Athero-ELAM). The detection of soluble/shed forms of these cell surface markers in serum/plasma is already being utilized as a surrogate index of endothelial dysfunction in certain clinical studies. The team proposes to further exploit these EC phenotypic markers as molecular targets for innovative, minimally invasive diagnostic and therapeutic applications.

Specific Aim 1: To develop a reproducible, robust small rodent model of endothelial activation that combines the use of adenoviral vectors (which can efficiently mediate high-level, localized expression of a given EC activation antigen, precisely where they are introduced into the vascular system), with a simple method of introduction into an anatomically defined vascular

bed. Note: all work involving rats in this overall project has been funded by sources other than the DoD, see Annual Progress Report October 1, 1998 through September 30, 1999.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Specific Aim 2: To apply radiolabeling method(s) that result in high specific activity of labeling of Fab'2 fragments of EC activation antigen-specific monoclonal antibodies, and validate the retention of specificity and avidity of binding to a cultured activated EC monolayer that expresses the target antigen(s) of interest.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Task 3: Develop a Computer Based Three-Dimensional Imaging Treatment Planning System to Drive an Endoscopically Placed, Miniature, Facial Skeletal Distraction Device.

Principal Investigator: *Leonard B. Kaban, MD, DMD and Maria Troulis, MD, MGH*

The significance of this project relates to the development of innovative, minimally invasive techniques for surgical treatment of patients with congenital and acquired craniomaxillofacial deformities. The combination of minimally invasive surgical techniques with the design and implementation of buried, miniature distractors guided by computer manipulated 3-D CT data, will increase operator and patient acceptance, and expand the applications of distraction osteogenesis (DO) to a variety of common craniomaxillofacial problems. There is no currently available system for surgical treatment of craniomaxillofacial deformities which links minimally invasive techniques, miniaturization, and a computer-based treatment-planning program. This concept is unique to the Massachusetts General Hospital, Skeletal Bone Research Center and the BWH Surgical Treatment Planning Laboratory project on DO.

Specific Aim 1: To develop a computer software application for the planning and simulation of an osteotomy and for analysis of the results. To accomplish this Specific Aim the following items will be addressed:

- To document reproducibility of the selected landmarks using both "Multiplanar" and "freehand" methods,
- To update the software and make it compatible with the new version of the "Slicer" and "Visualization Tool Kit" of the Surgical Planning Laboratory (SPL),
- To analyze skeletal changes in 25 pre and postoperative patients treated by distraction osteogenesis,
- To apply the software prospectively for treatment planning a selected variety of

- distraction cases, and
- To make the program more user-friendly for clinicians and accessible as a product.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Task 4: Virtual Fixtures for Robot-Assisted Minimally Invasive Cardiac Surgery

Principal Investigator: *Robert D. Howe, PhD*

This project develops new computer assistance techniques to improve efficiency and increase safety in robot-assisted minimally invasive surgery. Although these techniques will be applicable to a wide variety of robotically assisted surgical procedures, the immediate focus is coronary artery bypass graft (CABG) procedures, where robotic assistance enables minimally invasive techniques, but current robotic procedures are slow and cumbersome.

Specifically, this study develops image-guided virtual fixtures for the internal mammary harvest portion of robot-assisted CABG. In the experiments, the animal undergoes a CT scan before surgery. Small metal pins are inserted percutaneously between the ribs, to provide fixed landmarks for reference during surgery. The resulting image set is processed to define the location of the artery relative to the registration pins. In surgery, the surgeon brings the tip of a robot-mounted calibration instrument into contact with each of the pins. This permits the robot to determine the location of the pins, and thus the location of the artery from the CT image data. A virtual fixture constrains the instrument's motions, as commanded by the surgeon, to appropriate paths adjacent to the artery. In the next implementation, a surgical macro will move the robot along the path adjacent to each artery to dissect it free of the chest wall.

Key results: The CIMIT team is implementing a new approach that uses an electromagnetic tracker attached directly to the tip of the instrument. Based on this more accurate sensor, the team has developed a navigational aid that shows the location of the instrument tip relative to the internal mammary artery.

Specific Aim 1: Develop control techniques for "virtual fixtures" and "surgical macros" that assist the surgeon in guiding robotically positioned instruments.

Progress: The CIMIT team is implementing a new approach that uses an electromagnetic tracker attached directly to the tip of the instrument. Based on this more accurate sensor, the team has developed a navigational aid that shows the location of the instrument tip relative to the internal mammary artery.

Plan: The next step will be implementation of the virtual fixture based on this sensor, which will require interfacing the sensor with the ZEUS robot controller.

Specific Aim 2: Develop image-guided fixtures and macros that use preoperative 3-D patient images to help direct instruments to the appropriate tissues.

Progress: The team is testing the navigational aid described above *in vitro*.

Plan: *In vivo* animal trials of the navigational aid are planned for the immediate future. Once the electromagnetic tracker has been interfaced with the ZEUS controller, the team will proceed with tests of the virtual fixture using this more accurate sensing approach.

Specific Aim 3: Measure the performance of the enhanced system in surgical procedures on animal models in terms of: (i) the improvement in control of surgical tasks; and (ii) the precision attainable with these techniques.

Progress: No activity this year.

Plan: Following implementation of the navigational aid and the new virtual fixture control algorithm based on the electromagnetic tracker, the team will test accuracy and evaluate performance enhancement.

Task 5: Operating Room of the Future

Principal Investigator: David Rattner, M.D., MGH

The Massachusetts General Hospital (MGH) Surgical Executive Committee and CIMIT have been collaborating over the past year to design and build the Operating Room (OR of the Future). The team has grown in size to include 25 members with backgrounds in Surgery, Gynecology, Anesthesia, Nursing, Biomedical Engineering, Information Systems, Operating Room Management, Architecture, Engineering and Outcomes Measurement. Targeted industrial partners joined the team and are listed below.

The overall goal of the Operating Room of the Future (ORF) project is to develop new surgical equipment, procedures and processes that will result in improved patient outcomes, operating room efficiency, or both. The ORF project has sought to establish links to both industry partners and academic researchers who are developing these new technologies, in order to make the ORF surgical suite a comprehensive test platform for product and process development. Substantial progress has already been made towards creating a prototype operating room which incorporates modular equipment, new surgical information systems, and new approaches to process flow.

Specific Aim 1: To design and build a novel Operating Room (OR of the Future):

- Team formation, finalizing goals,
- Establishing Industry Collaborators,
- Testing, Finalizing Room Design
- Identifying Needs, Methods of Tracking Equipment and People
- Identifying Needs and Facilitating Design of Information Integration

Team formation, finalizing goals

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Establishing Industry Collaborators

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Testing, Finalizing Room Design

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Identifying Needs, Methods of Tracking Equipment and People

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Identifying Needs and Facilitating Design of Information Integration

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue to design and build the Operating Room of the Future under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 2: To develop and utilize computer simulation models in order to evaluate the complex and changing systems of the Operating Room of the Future.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue to design and build the Operating Room of the Future under Cooperative Agreement No. DAMD17-02-2-0006.

2.3 IMAGE GUIDED THERAPY

Virtually every device that supports minimally invasive procedures relies on processed images. These images provide preoperative data and guide surgery. While already useful for brain, spine and musculoskeletal surgery, current systems have limitations: the integration is awkward, they slow down the procedures they are intended to facilitate, and data preparation in clinical setting is too time consuming. To overcome such limitations Image Guided Therapy Enabling Technology is developing robust and flexible algorithms that incorporate knowledge about anatomy and pathology and provide intuitive user interfaces.

Task 1: MRI-guided Focused Ultrasound Treatment of Breast Cancer

Principal Investigator: Ferenc Jolesz, MD, BWH

The overall goal of this project is to develop a magnetic resonance imaging (MRI) guided focused ultrasound system for thermal coagulation of breast cancer. The first accomplishment for making clinical breast treatments practical is to develop and test phased array ultrasound applicators that allow the focal spot size to be increased. This is needed for two reasons: A large focal spot allows the tumors to be coagulated in a shorter time, making the treatment time practical. It also reduces the nonuniformities in the temperature field thus assuring better treatment response. Overall, the team has made significant progress using an animal model that will make noninvasive MRI guided thermal coagulation of breast tumors practical for clinical testing.

To study this hypothesis in a clinical setting the team needs to develop sonication and MRI thermometry methods for practical treatments and to test them in animal experiments.

Key Results: The several phased array systems were tested using an animal model and the results were used to develop the final 208-channel phased array system in collaboration with a commercial manufacturer. The results are good, demonstrating the ability of the system to coagulate tumor tissue similar in size and location to breast cancer.

Specific Aim 1: Develop treatment-plan procedures utilizing 3D-MRI information to determine the target volume and execute treatment:

- To evaluate the feasibility of inducing temperatures between 60 and 100°C in tissue volumes required for breast cancer treatments during a 10-60 second sonication.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 2: Study the accuracy of MRI-derived temperature history for calculating the thermal exposure of tissue.

The goal of this Specific Aim is to test and evaluate the feasibility of using MRI thermometry to estimate the temperature and thermal dose induced by the sonifications and to test its accuracy. The team used *in vivo* animal tissues for these tests.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 3: Establish the thermal exposure required to assure complete tumor coagulation.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 4: To test Specific Aim 3 in implanted rabbit tumors.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 5: To evaluate the influence of fat and tissue motion on the MRI dosimetry.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Task 2: Early Detection and Ablation of Epithelial Cancers

Principal Investigator: *Norman S. Nishioka, MD, MGH*

Subtask 1: ALA Enhanced Fluorescence Imaging of Barrett's Epithelium

Note: We will be forwarding written correspondence regarding our intention to withdraw this study.

This study will investigate the use of aminolevulinic acid (ALA) to enhance the fluorescence signal from dysplastic cells in the esophagus in the specific case of Barrett's esophagus. High-grade dysplasia in Barrett's esophagus has been known to progress into adenocarcinoma. Patients diagnosed with Barrett's usually require long-term endoscopic surveillance. While

Barrett's epithelium is easily detected on endoscopy, regions of dysplasia cannot be easily visualized with white light. The results of previous studies have demonstrated the potential of this method to identify and localize pre-malignant regions of the esophagus that cannot be seen during routine endoscopy. This study will determine the accuracy of orally administered ALA in marking dysplasia and develop, test and improve the endoscopic system for fluorescence detection in the esophagus.

Specific Aim 1: Determine the accuracy of orally administered ALA for marking dysplasia occurring in Barrett's esophagus.

Progress: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Plan: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Subtask 2: OCT Imaging of Esophageal Lesions

Principal Investigator: *Norman S. Nishioka, MD, MGH*

Note: We will be forwarding written correspondence regarding our intention to withdraw this study.

The goal of this project was to determine the clinical utility of OCT for imaging lesions in the gastrointestinal (GI) tract. Modern gastrointestinal endoscopy is a potent diagnostic and therapeutic technique for the management of a wide variety of GI disorders. However, one limitation of conventional endoscopy is the inability to visualize structures beneath the mucosal surface of the GI tract. The advent of endoscopic ultrasound has made it possible to visualize subsurface structures in many settings, but the instrumentation is expensive and the spatial resolution is limited by the transducer operating frequency (<30 MHz). Optical coherence tomography (OCT) is an alternate technique for obtaining high-resolution cross-sectional images of tissue. The operating principles of OCT are analogous to ultrasound except that light waves are used to image tissue rather than acoustic waves. The spatial resolution of OCT is approximately 10 times better than that of the best ultrasound devices.

Specific Aim 1: Perform a pilot trial of OCT in unselected patients undergoing upper endoscopy to assess the spatial resolution and clinical usability of the present system.

Progress: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Plan: Project completed. See Quarterly Progress Report October 1, 1999 through December 31, 1999.

Task 3: Segmentation of Bone from CT and Vessels from MRA Data

Principal Investigator: Carl-Fredrik Westin, PhD and Ron Kikinis, MD, BWH

The broad goal of this project is to improve the way that information from medical image data is extracted. The project is a continuation of our ongoing effort to develop new technologies to improve efficiency and specificity in creating patient specific anatomical 3D models for surgery simulation, surgical planning, and image-guided intervention.

Key Results: The team has introduced a new image feature, based on local phase, which describes local edge symmetry independent of absolute gray value. The phase is a natural by-product from the filters used in the adaptive filtering scheme presented last year in the project. Because phase is amplitude invariant, the measurements are robust with respect to smooth variations, such as bias field inhomogeneities present in all MR images. In order to enable validation of the phase-wire segmentation software, a system has been created that continuously records user interaction and automatically generates a database containing the number of user interactions, such as mouse events, and time stamps from various editing modules.

Specific Aim 1: To implement a data enhancement scheme for segmentation of bone from CT and vessels from MRA.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To implement a data enhancement scheme for segmentation of bone from CT and vessels from MRA.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3: Optimization and Validation: to quantitatively validate and optimize the automated segmentation method results.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3.1: Optimization and Validation: validation of phase-wire segmentation software.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 4: Extend out current implementation of adaptive filtering to incorporate interpolation to a finer grid.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 5: To develop a segmentation model based on the team's experience on adaptive filtering and surface evolution.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Task 4: Real-time Registration of Intra-operative Ultrasound with Pre-operative CT/MR for Image Guided Therapy

Principal Investigator: *Eric Grimson, PhD, Massachusetts Institute of Technology (MIT), Cambridge, MA*

The utility of minimally invasive therapy depends, in no small measure, on the ability to precisely deliver therapy to the targeted site. The efficacy of image-guided therapies is now well documented in the literature for such applications as tissue biopsy, cryotherapy, brachytherapy, and energy delivery. For the most part, however, image guidance requires expensive intra-operative equipment (e.g., intra-operative MRI), ionizing radiation (e.g., fluoroscopy, CT), or is limited to surface (e.g., luminal) imaging of areas accessible through videoendoscopic tools. Although inexpensive, non-ionizing, subsurface-capable, and portable, ultrasound imaging has not found the widespread usage that one might expect, due largely to the poor-contrast, specular noise, and unintuitive nature of ultrasound imagery. In this proposal the team aimed to demonstrate a novel new method for improving the visualization quality of intra-operative ultrasound imagery. Specifically, because of the overwhelming preference of users for high-contrast CT/MR imagery, and since such imagery are frequently acquired pre-operatively, the team aimed to demonstrate the ability to register these high contrast pre-operative imagery to yield the same view as the intra-operative ultrasound. The approach enabled, effectively, an intra-operative CT/MR imagery from which image guidance can be performed, but without incurring the costs and risks associated with continuous CT/MR imaging.

Specific Aim 1: Demonstrate the ability to register pre-operative CT/MR, in a non-real-time manner, so that point-to-point correspondence to an intra-operative ultrasound can be obtained.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Specific Aim 1.1: Select a set of surface points from MR/CT, and use ICP to match the points to edges in ultrasound. This result provides an initial correspondence between the two data sets.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Specific Aim 1.2: Explore numerous variations on polynomial warping methods which included the following: variation of the number of corresponding points; variation of polynomial order; variation of the point set distribution; and error verification to measure sensitivity in our computed registration errors.

Progress: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

Plan: Project completed. See Annual Progress Report October 1, 1999 through September 30, 2000.

2.4 TISSUE ENGINEERING

The field of Tissue Engineering is now maturing and undergoing explosive growth. Virtually every tissue and organ of the body has been studied. Many tissue engineering technologies are becoming available for human use. Over time, several techniques to engineer new living tissue have been studied. Technologies include the use of growth factors to stimulate wound repair and regeneration, techniques of guided tissue regeneration using non-living matrices to guide new tissue development, cell transplantation, and cell transplantation on matrices. Recent studies in stem cell biology has led to studies of populations primordial cells, stem cells or embryonic stem cells to use in tissue engineering approaches.

Task 1: Degradable Conductive Polymers

Principal Investigator: Robert Langer, ScD, MIT

Electroactive polymers, which constitute a unique class of synthetic polymers, possess the ability to inter-convert chemical, mechanical, thermal and optical perturbations into tiny electrical currents. This property can be exploited to play an important role in the interfacing of the external environment with biological systems. Electronically conductive polymers are especially attractive in that, they can not only be employed as guidance channels or substrates for tissue culture but can also potentially be utilized as a medium to subject the adhered tissue (cells) to an electrical stimulus. The team has shown that electrical stimulation of neuronal and mesenchymal progenitor cells adhered to conductive oxidized polypyrrole (Ppy) substrates, in presence of soluble morphogens and growth factors can aid in the lineage specific differentiation of these cells. In its traditional chemical form oxidized Ppy is non-degradable and is minimally processible. A more processible and bioerodible Ppy would be particularly important for applications wherein a PPy coating is used to alter the surface characteristics or tissue response to a prosthetic for a well-defined period such as coating of a vascular stent to minimize smooth muscle proliferation and restenosis. One can also envision coating of metal or carbon composite or other polymeric orthopedic prosthesis with conductive polymers such as polypyrrole to improve tissue compatibility and adherence of the implant to surrounding tissue. Furthermore, from a tissue-engineering standpoint, it would be ideal if the conductive polymer matrix served as a template for the desired period and underwent degradation thereafter thus eliminating any potential long-term undesirable tissue response.

Key Results: The team has synthesized and characterized a novel family of Ppy's. These polymers have been shown to undergo dissolution/erosion under physiologically relevant conditions *in vitro*. The team has also demonstrated that the erosion rate of these substrates may be modulated by the judicious choice of the ionizable end group in the alkyl moiety at the beta position on the pyrrole ring.

Specific Aim 1: To synthesize degradable analogs of the conductive polymer PPy, as well as water soluble analogs, and to study the degradation and cytocompatibility characteristics of these polymers.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: Project completed.

Task 2: Polymer-based Gene Delivery Platform

Principal Investigator: Robert Langer, ScD, MIT

Safe and effective pharmaceutical delivery systems for DNA will need to be developed in order for the field of gene therapy to advance further into the clinic. For local therapeutic levels of protein to be generated, high levels of gene expression within a desired subset of cells is generally required. To this end, the local delivery of gene therapeutics via minimally invasive modalities, such as catheters or endoscopes could lead to important advances, because these techniques can be used to administer DNA (and thus therapeutic protein) at desired sites rather than administering them systemically.

The long-term goal of this project has been to create a safe synthetic polymeric gene delivery system with high transfection efficiency for local delivery of plasmid DNA. The work conducted toward Specific Aim 1 of the current grant period has been directed toward the continued development of new polymeric "proton sponge" materials and the development of a mechanistic understanding through which these materials mediate transfection. The team is nearing completion of a collaborative effort with investigators at the University of California at San Francisco to investigate their most promising polymers for the delivery of therapeutic HIV vaccines in mouse models. The work conducted toward Specific Aim 2 in recent quarters has been directed toward the development of a parallel synthesis and screening strategy for the discovery of new degradable polycations useful as gene delivery vectors and pH-responsive materials for enhanced intracellular delivery.

Key Results: The team has continued development on the first accelerated discovery approach for finding synthetic transfection vectors. This year, the team has begun the synthesis of a library containing up to 3,500 individual polymers. In the near future, this library will be screened for gene transfer efficiency. Work has also been done to further characterize the polymers in the original poly(β -amino ester) library. The library was characterized along the following dimensions: (1) effective diameter of polymer-DNA complexes, (2) zeta potential of polymer-DNA complexes, and (3) relative uptake of complexes by 3T3 cells.

Specific Aim 1: To synthesize a polymer-based gene delivery system that on the molecular level mimics viruses.

Progress: As discussed in the previous quarter, the team initiated a collaborative project with Prof. Chris Locher in the Department of Virology at the University of California at San Francisco (currently at Maxygen, Inc.) to conduct a head-to-head *in vivo* comparison of naked DNA, liposome formulations, and the team's "proton sponge" polymers using a therapeutic HIV vaccine and a mouse model. Based on experiments concluded this year, Prof. Locher has recently submitted a paper for publication.

Specific Aim 2: To synthesize new degradable polymers for use as gene transfer vectors, and to investigate the degradability, cytotoxicity, and ability of these polymers to condense and/or encapsulate DNA into particles suitable for transfection.

Progress: Last quarter, the team used preliminary high-throughput screening assays to identify two polymers that yield gene expression in model cell lines at levels surpassing those of both PEI and Lipofectamine 2000, two leading polymeric and liposomal transfection agents. The team continues to investigate the library that yielded these polymers in order to understand the structure/property relationships for these polymers and other members of the polymer library. This year, the team has characterized this library along the following dimensions: (1) effective diameter of polymer-DNA complexes, (2) zeta potential of polymer-DNA complexes, and (3) relative uptake of complexes by 3T3 cells. See Figures 1-3 below.

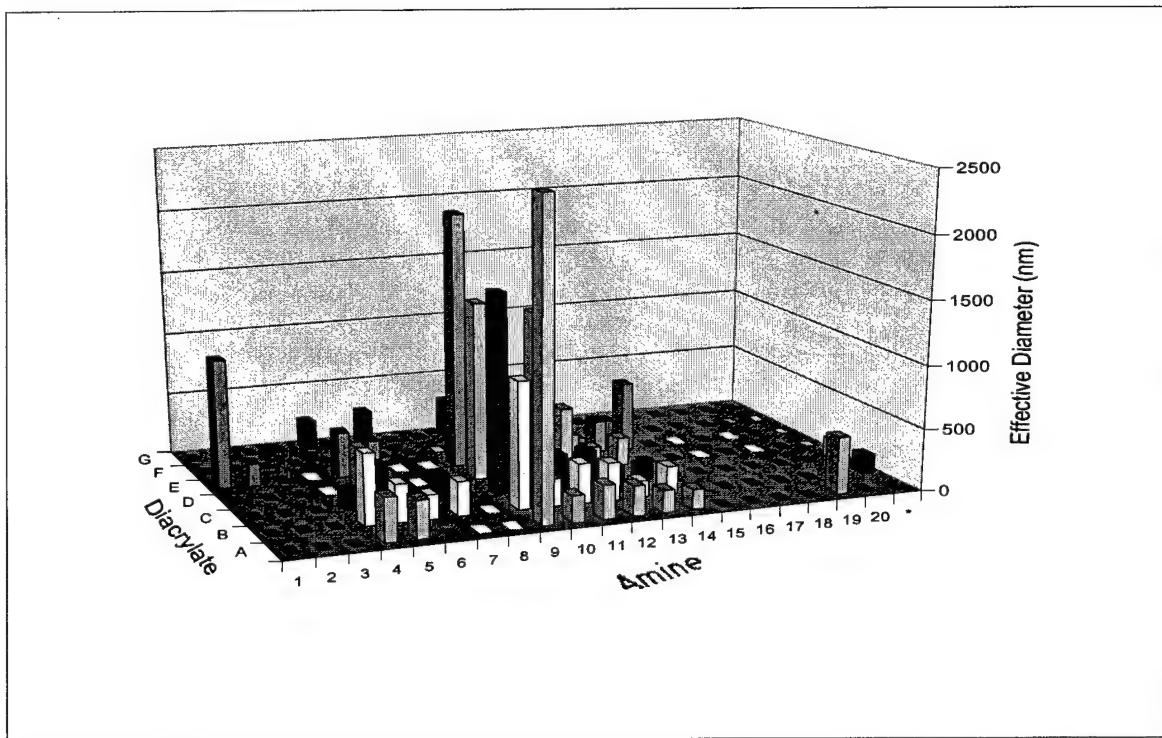


Figure 1: Effective Diameter as a function of polymer structure. Complexes were formed at DNA:polymer weight ratios of 1:20. Effective diameter determined using laser-light scattering in 10 mM Hepes buffer pH 7.2.

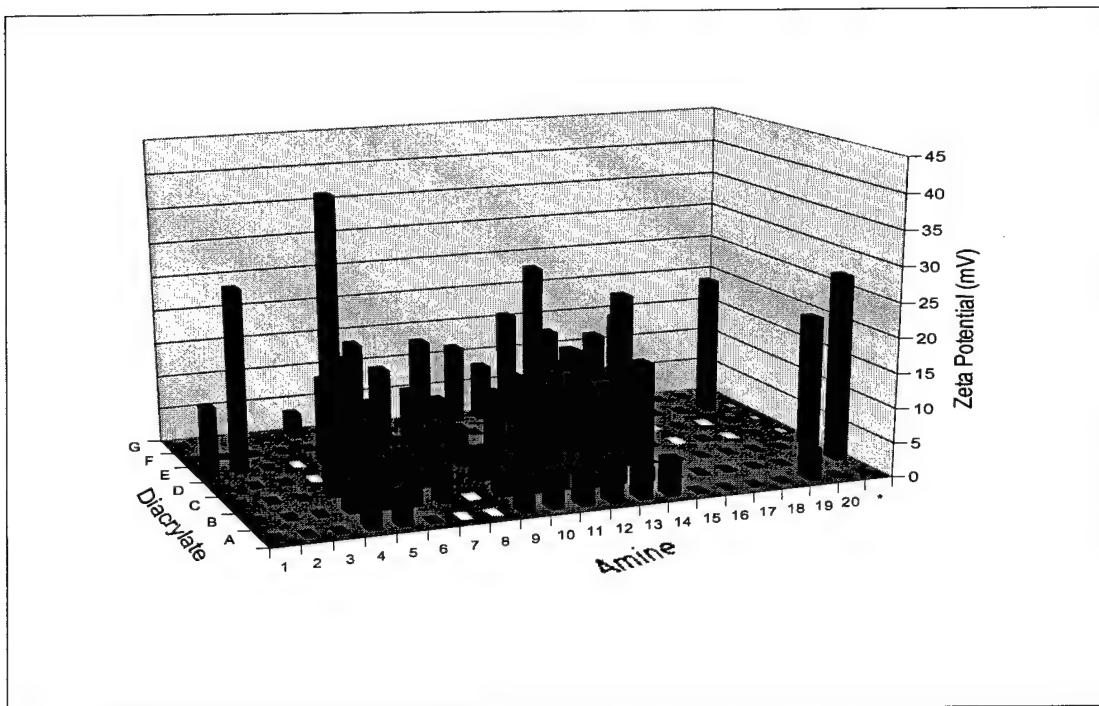


Figure 2: Zeta potential of DNA-polymer complexes as a function of polymer structure. Red bars indicate positive zeta potential values, while black bars indicate negative zeta potential values.

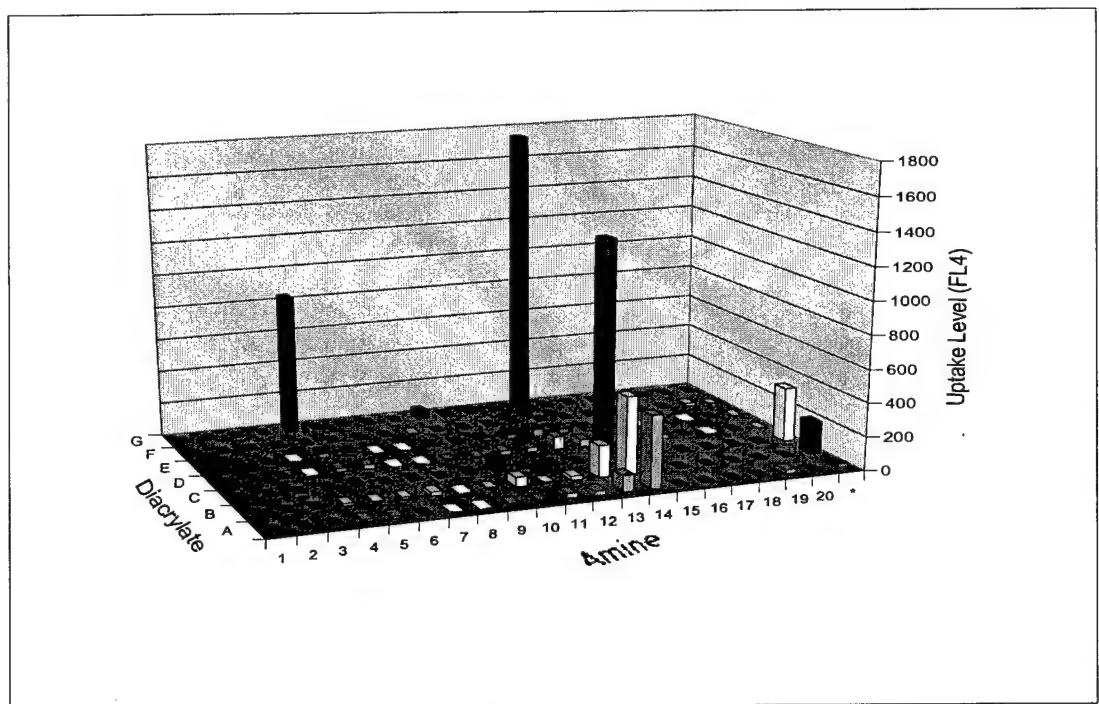


Figure 3: Relative uptake level of DNA-polymer complexes by NIH 3T3 cells as a function of polymer structure. Red bars indicate positive zeta potential values, while black bars indicate negative zeta potential values.

The team has also initiated the synthesis of larger libraries of polymers (up to 3,500 chemically distinct structures) based on their initial technology. In the near future, these libraries will be screened to identify polymers that mediate high levels of gene transfer.

Plan: To continue new research in Degradable Conductive Polymers under Cooperative Agreement No. DAMD17-02-2-0006.

Task 3: Transdermal Drug Delivery and Chemical Sensing for Neonates using Skin Electroporation

Principal Investigator: *James C. Weaver, PhD, MIT*

Our research into an improved method of transdermal drug delivery has yielded two major results. First, a new method for creating transdermal microconduits has been developed, which will be reported in a paper to be submitted for publication. Microconduits can be used for drug delivery and for interstitial fluid sampling. Second, a new method for carrying out function-based simulation of transport of charge, heat and molecules has been developed, and this will also be reported in a manuscript that is being written for submission to a scientific journal. The simulation has the potential to increase the productivity of research and development of minimally invasive technology, such as drug delivery protocols and devices that interface with tissue. This new, presently unpublished method was partially developed during our investigation of the skin's response to electrical pulses.

While investigating the optimization of microconduit creation in the skin's stratum corneum (SC), the team has continued to seek understanding about how the multilamellar bilayer membranes within the SC are electroporated. This remains key to understanding how safe keratolytic agents are delivered into the SC, and how brief, highly localized heating takes place.

Key Results: During the past year new approach to computer simulation of spatially complex systems was identified. The team has obtained very encouraging results for a simulation of the transport of potent agents through the skin due to exposure of a small amount of the compound to the surface of the skin.

Specific Aim 1: Optimize parameters for creation of microconduits in hairless rat skin *in vitro*.

Specific Aim 2: Determine transdermal transport of aqueous solution through microconduits *in vivo* in hairless rats.

Specific Aim 3: Creation and partial optimization of microconduits in neonatal skin *in vitro*.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Task 4: Synthesize Vascularized Living Systems from the Platform of Two-Dimensional Silicon Microfabrication Technologies and Adapt to Three-Dimensional Living Devices
Principal Investigator: Joseph Vacanti, MD, MGH

See section 1.2, Highlight Project on page 11.

Task 5: Synthesize Vascularized Living Systems from the Platform of Three-Dimensional Printing Technology

Principal Investigator: Joseph Vacanti, MD, MGH and Jeffrey Borenstein, PhD, Draper Laboratory, (DL), Cambridge, MA

Significant progress in the development of new microfluidic designs, materials and fabrication processes has been made in the previous quarter. New fluidic network designs for the extension of existing 2D networks into the third dimension have been generated, and preliminary fabrication work on the 3D networks has begun. A novel material known as biorubber, recently developed by Professor Robert Langer's group at MIT, has been tested using microfabrication processes. Finally, significant progress on the development of high-resolution microfabrication processes for biodegradable polymers has been made.

Key Results: Over the past year, the new designs described in the last progress report have become the baseline for cell culture studies. These designs, labeled TESTNET0, TESTNET1 and TESTNET2, are smaller, more modular and simpler to produce. They are based upon low-cost layout and mask-making technology and provide for uniform flow.

Specific Aim 1: Design and fabricate silicon and Pyrex based systems providing an array of etched channels to act as a mold for generating a living network in two dimensions. To accomplish this Specific Aim the following items will be addressed:

- Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold,
- Design bioreactors to house the device during tissue formation and folding,
- Develop assays to study the generation of tissue and its histologic, biomechanical, and biochemical parameters,
- Investigate mechanisms of tissue development using molecular markers for gene developmental programs and programs of wound healing and regeneration, and
- Begin animal implantation studies to begin to understand perfusion, survival, and function of the living device, and
- Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold.

Design and fabricate silicon and pyrex based systems providing an array of etched channels to act as a mold for generating a living network in 2 dimensions

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Tissue Engineering under Cooperative Agreement No. DAMD17-02-2-0006.

Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new research in Tissue Engineering under Cooperative Agreement No. DAMD17-02-2-0006.

Task 6: Minimally Invasive Meniscal Repair with Tissue Engineered Cartilage

Principal Investigator: Thomas J. Gill, MD and David J. Zaleske, MD, MGH

Recent findings demonstrate that a cell-based therapy could be one therapeutic approach for repairing tears in the avascular zone of the knee meniscus cartilage. In previous studies in the nude mouse model, articular chondrocytes seeded onto a devitalized meniscal cartilage scaffold were able to bond the edges of a meniscal tear. Those studies were performed in a vascular subcutaneous environment, which is different from the avascular articular environment of the knee joint. The studies performed over the past year demonstrated that the same goal could be achieved in the articular environment in a large animal model. The results of the first year of investigation demonstrated that this tissue engineered approach could repair the knee meniscus when a lesion involves the avascular inner third. Although further investigation is still needed to define the best delivery material and the best pre-seeding conditions of the reparative cells onto such a scaffold, the team believes that a clinically applicable approach combining this technique with arthroscopic surgery might be soon developed.

The Specific Aims of this project are: 1) to demonstrate that chondrocytes, seeded onto a matrix scaffold, can be used as valid therapeutic approach to achieve a secure meniscus repair in a preclinical orthotopic model; and 2) to investigate other cell sources and different absorbable materials for cell scaffolding to accomplish a minimally invasive meniscus repair technique. In previous studies in the nude mouse model, articular chondrocytes seeded onto a devitalized meniscal cartilage scaffold were able to bond the edges of a meniscal tear. Results from these studies demonstrate that a cell-based therapy could be a useful therapeutic approach for repairing tears in the avascular zone of the knee meniscus cartilage.

Key Results: Studies performed over the past year demonstrated that a cell-based therapeutic approach can be used in the articular environment in a large animal model of meniscal tears. Further investigation during the second year sought to define the best delivery material and the best pre-seeding conditions of the reparative cells onto candidate scaffolds. A clinically applicable approach combining this technique with arthroscopic surgery might be developed based on these studies.

Specific Aim 1: To demonstrate that chondrocytes, seeded onto a matrix scaffold, can be used as valid therapeutic approach to achieve a secure meniscus repair in a preclinical orthotopic model.

Rationale: During the past year, the team has demonstrated meniscal healing in a nude mouse model, using articular cartilage chondrocytes as the cells source and devitalized meniscal chips as structural support for chondrocytes. The central hypothesis of this project is that a lesion in the meniscus can be repaired using isolated autologous cells seeded onto a scaffold material. The scaffold could be allogeneic devitalized meniscal tissue or other synthetic materials to be investigated. The cells could be chondrocytes or other cell population, stimulated to chondrogenic differentiation. The cell-seeded construct would be then interposed in the meniscal lesion and secured in place. Healing would be achieved by the bonding capabilities of the cells. The goal of this section will be to develop and refine the model for creating a reproducible meniscal injury in the medial meniscus of pigs. Once this goal is achieved, new constructs or variables to be investigated in subsequent stages of the project will be tested in the same fashion for consistency.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 2: To investigate other cell sources and different absorbable materials for cell scaffolding to accomplish a minimally invasive meniscus repair technique.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Task 7: Development of a Novel *in vivo* Recombinant Protein Delivery Device Designed to Regress Abnormal Tissue: Recombinant Human Müllerian Inhibiting Substance (rhMIS) Producing Cells on Biodegradable Matrices

Principal Investigator: David T. MacLaughlin, PhD, MGH

A major problem impeding progress in using complex human proteins as therapeutic agents against disease including cancer is producing sufficient quantities for use in a cost-effective manner and the development of a suitable and effective system to deliver these proteins to patients. Most of these proteins are complex macromolecules consisting of subunits and/or covalently attached substituent groups. In Nature they are produced in extremely small quantities and it is impossible to purify enough for use in the clinic. Therefore, there are significant problems to overcome before the cost-effective production of sufficient quantities of highly purified proteins as drugs can be accomplished. Modern cloning strategies have created organisms that produce large quantities of the proteins that still needed to be purified for clinical use. These methods are expensive, have modest yields and they reduce biological potency. Our project is designed to eliminate both the requirement for *in vitro* production facilities and the need to purify the proteins. We used Müllerian Inhibiting Substance (MIS) as a model protein and the treatment of ovarian cancers *in vivo* as a biological assay to test the hypothesis that bio-engineered implantable tissue could be used as a drug delivery system.

Key Results: Resorbable polyglycolic acid biopolymer matrices impregnated with cells transfected with the MIS gene were successfully implanted in over 80 immuno-compromised mice and bioactive MIS produced and absorbed by the blood stream. The effect of different sized biopolymer implants on the resulting serum MIS concentrations was also determined.

Specific Aim 1: Determine *in vivo* pharmacokinetics of recombinant human MIS produced on degradable biopolymer matrices implanted into SCID mice by transfected clonal CHO B9 cells.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new MIS research under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 2: Determine if the recombinant human MIS produced by transfected CHO B9 cells inhibit growth of human ovarian carcinoma cell lines transplanted beneath the renal capsule of SCID mice.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue new MIS research under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 3: Harvest autologous fibroblasts from patients with ovarian cancer, transfect them with the human MIS cDNA, and re-implant mesh impregnated with the patients own MIS producing transfected cells into the peritoneal cavity, using laparoscopic minimally invasive techniques.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue new MIS research under Cooperative Agreement No. DAMD17-02-2-0006.

Task 8: Determine the Role of Mesenchymal Stem Cells in Fetal Tissue Engineering

Principal Investigator: *N. Scott Adzick, MD, University of Pennsylvania (UPenn) and Children's Hospital of Philadelphia (CHOP) and Alan W. Flake, MD, CHOP*

The overall goal of this research is to define the tissue engineering potential of mesenchymal stem cells (MSC). During this past year, the team has made considerable progress in isolating, expanding, and documenting the *in vitro* multipotential differentiative capacity of fetal liver derived mesenchymal stem cells in sheep. The team has also established site-specific differentiation of adult bone marrow derived human mesenchymal stem cells in the fetal sheep model after prenatal systemic administration.

The team has successfully tissue engineered bone marrow using principles derived from known mesenchymal stem cell biology and tissue engineering. These accomplishments have been documented in a number of oral and poster presentations at national meetings as well as in manuscripts, either published or in progress.

The team has formed collaborations with Dr. Catherine Verfaillie at the University of Minnesota (human and mouse MSCs), Dr. Johnny Huard at the University of Pittsburgh (muscle progenitor cells), and Dr. Paul Simmons from Melbourne (Mouse MSC) to investigate the relative merits of these various promising cells in our fetal models. In addition, the team is applying their low density culture techniques to sheep fetal liver derived MSC to isolate a small phenotype fetal cell with multipotential capacity. Simultaneously, the team has been developing lentiviral vectors to apply to these cells to manipulate their *in vivo* biology. The team has developed lentiviral vectors for MyoD (drives MSCs toward muscle differentiation), Pax7 (an upstream transcription factor from MyoD which regulates MSC to muscle progenitor differentiation), and are working on a

vector for Hox4B (a stem cell proliferation regulatory homeobox transcription factor) which the team will test *in vivo* in future experiments.

Key Results: The team made significant progress toward the clinical utilization of mesenchymal stem cells. Due to progress from other investigators in the field, it is clear that a mesenchymal stem cell of small phenotype, rather than the large fibroblastic phenotype used in our previous studies, has significantly greater differentiative capacity *in vitro*, and contains a higher frequency of CFU-f forming cells.

Specific Aim 1: Determine the multipotential differentiation of sheep mesenchymal stem cells *in vitro*.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 2: Determine site-specific differentiation of mesenchymal stem cells in the developing fetus.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 3: Establish clinically applicable methods to isolate and expand mesenchymal stem cells in the sheep.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Specific Aim 4: Apply the principles of mesenchymal stem cell differentiation to the concept of tissue engineering by organizing mesenchymal stem cells on a biodegradable polymer and implanting the construct *in vivo* for tissue reconstruction.

Progress: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 through September 30, 2001.

2.5 SIMULATION

The CIMIT Simulation Program has parallel primary thrusts: (1) developing the basic science required for realistic computer-based medical simulation and (2) validating state of the art simulations through the construction and testing of demonstration systems. The Program's principal activities involve measurement of tissue characteristics, integration of haptics into simulation, and realistic representation of medical procedures for training, device prototyping and procedural development.

Task 1: Discover Enabling Technologies for Medical Simulation

Principal Investigator: Steven L. Dawson, MD, MGH

The CIMIT Simulation Group continued to make progress on multiple fronts during the past year. On the research side, the team has begun design of the CAML framework for simulation development, began collaborations on source code sharing with Stanford University, and started new initiatives in validation of the VIRGIL® system and surgical skills trainers. On the applications side, the team has redesigned the VIRGIL Training System infrastructure to improve reliability and robustness, the team has designed a skills assessment training system. Also, the team has installed the equipment needed to provide on-site manufacturing capability on the Lansdowne Street facility.

From the intellectual property perspective, the team has continued negotiations with Limbs and Things on patent protection, and we were notified that the VIRGIL trademark has been accepted, so that VIRGIL is now VIRGIL®. The technological advances that VIRGIL® represents attracted the attention of Ascension Technologies, the manufacturer of the mini-BIRD tracking devices used in the system. As a result of our creative use of tracking, Ascension has joined the CIMIT Industrial Liaison Program, and will be working closely with us to further refine the abilities of position tracking tools in medical applications.

Together with TATRC, the team participated in the 2002 Medicine Meets Virtual Reality meeting in Newport Beach, California, demonstrating VIRGIL® to computer scientists and simulation developers as a member of the TATRC demonstration booth. Group members presented at the TATRC principal investigator's review and the Simulation Challenges Workshop, and presented an original scientific paper on tissue property measurements ("In vivo measurement of solid organ visco-elastic properties").

While at the MMVR meeting, the team convened two separate sessions of the CAML consortium, bringing together representatives from MGH, the National Center for Medical Simulation, the Stanford CASS group, the National Biocomputation Center at Stanford, ETH Zurich, and the University of Tubingen.

Over the last year, group members have submitted two scientific papers to the Medical Image Computing and Computer Aided Interventions (MICCAI) 2002 meeting. We anticipate that these works will be accepted for this rigorous and prestigious international meeting. Mark Ottensmeyer collaborated with Cynthia Bruyns at the National Biocomputation Center at Stanford University on a work comparing *in vitro* soft tissue properties and finite element models in a virtual animal model ("The Development of a Physically Based Virtual Animal Model using

Soft-Tissue Parameter Testing"). We also submitted a paper that presents the early results of our new initiative in validation of surgical skills ("Metrics for Laparoscopic Skills Training: The Weakest Link").

In February, Daniel Kalanovic, a research surgeon from Tubingen, Germany began a six-month research fellowship with the Simulation Group, funded by a grant from the German government. Daniel will be working with Mark Ottensmeyer, comparing experimental methods and results from the Tubingen group with our results.

Lastly, the CIMIT Simulation team hosted a visit to VIRGIL® by Representatives Murtha, Capuano, and Lynch from the US Congress, during their CIMIT visit on March 18th.

Specific Aim 1: Tissue Modeling - Develop tools capable of *in vivo* measurement of soft tissue characteristics, including:

- Haptics-Enabled force feedback of tissue data to render tissue manipulation realistic,
- Geometric modeling and visual feedback - recreate on the monitor screen a believable representation of tissue-tool interactions,
- Integration of physiology into computerized representations of procedures, and
- Development of a common anatomic modeling language (CAML) to achieve integration of physiology into computerized representations.

Progress: Project completed.

Plan: To continue Medical Simulation research under Cooperative Agreement No. DAMD17-02-2-0006.

2.6 NEW INITIATIVES

The New Initiatives Enabling Technology provides an incubator for approaches to clinical problems that are likely to evolve into novel therapies and outcomes analyses that can be applied to a variety of medical problems. As these approaches mature, they will be made available to other Enabling Technologies.

Task 1: Lung Volume Reduction Using a Bronchoscopic Approach

Principal Investigator: Edward P. Ingenito, MD, BWH

The objective of lung volume reduction is to eliminate dysfunctional, overinflated regions of the lung. Results similar to surgical resection have been obtained by plication and stapling without tissue removal, as well as by laser directed tissue ablation. These observations suggest that removal of the dysfunctional tissue is not required. A procedure that eliminated the participation of dysfunctional tissue in the breathing process would suffice.

There have been no detailed studies on the lung mechanical effects of experimental emphysema in large animals. It is useful to know the specific changes in lung mechanics with emphysema induction to deploy the animal model for studies of novel emphysema interventions. Specifically, the team wished to understand the effects of papain to induce emphysema on airway and tissue resistance and elastance, since diseases such as emphysema may harbor both parenchymal and airway abnormalities concomitantly. To do so, the team employed a method of optimal waveform ventilation for measurement of dynamic airway and tissue mechanics, and static measurements of elastic recoil and functional residual capacity. The goal was to demonstrate that parenchymal disease induced by papain was similar to human emphysema. Hence, this project entailed two scientifically novel features: 1) the development of a reproducible model of diffuse emphysema in sheep using aerosols of papain, and 2) the characterization of the disease process using optimal waveform ventilation (OWV) in addition to static mechanics.

Specific Aim 1: To compare short term (1 month) and long term (3 month) survival, physiological responses, surgical complications and lung histopathology in control sheep (untreated, non-emphysema) following either standard surgical plication lung volume reduction or bronchoscopic lung volume reduction (BVR).

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To compare short and long term survival, physiological responses, complications, and lung histopathology in sheep with emphysema (generated by papain exposure) treated either with SPVR or BVR.

Volume reduction therapy (VRT) for emphysema involves removal of hyper-expanded, dysfunctional lung, which increases recoil, improves tethering, and recruits previously

compressed lung. This has traditionally been accomplished by surgical means. The team describes a bronchoscopic method of VRT in which fibrin glue containing pro-fibrotic growth factors is used to collapse and scar emphysematous lung.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Task 2: Outcome Assessment in Menorrhagia

Principal Investigator: Johanna Bosch, PhD, MGH

Minimally invasive treatments have been developed to treat menorrhagia. Evaluation studies comparing these therapies with traditionally performed therapies, such as hysterectomy, are needed to help physicians, patients and policy makers to make informed decisions. Therefore, appropriate (i.e., preference based and from the community at large) quality-of-life data and the assessed relative benefits and cost-effectiveness of new therapies are needed. In this study, we assess the quality of life in women with menorrhagia using existing utility assessment instruments, a simple preference-based instrument (the binary-gamble method) will be developed further to assess community preferences, and a decision model to perform cost-effectiveness analyses of minimally invasive therapies for menorrhagia is being developed.

Key Results: The CIMIT team has developed a self-administered questionnaire including the Health Utilities Index and EuroQol-5D to collect quality-of-life data in patients with menorrhagia. Upon the patient survey and its data analyses, the binary-gamble method will be used to assess community preferences for menorrhagia in a sample of the general population.

Specific Aim 1: To assess quality of life in women with menorrhagia using the HUI and the EuroQol-5D.

Progress: Currently, the CIMIT team has developed the questionnaire with the research staff at the DATA Group, and research staff in the Department of Gynecology to evaluate quality of life, general health status, and out-of-pocket and time costs in patients with menorrhagia. Innovative quality-of-life methods have been incorporated into the cross-sectional survey. Because standard quality-of-life instruments such as EuroQol, HUI, or the visual analogue scale are intended for chronic conditions, they are unsuitable for use for patients with menorrhagia, a condition that primarily affects women in monthly episodes. A modified version of these instruments is being used and the feasibility of this type of research will be assessed. We believe that this type of methodology can be applied to other episodic health conditions as well. The research staff at the Department of Gynecology has recently moved to another hospital, which has delayed the recruitment of patients. The team will now seek final DoD approval of the staff relocation before initiating the study.

Two different quality-of-life questionnaires have been composed. One questionnaire includes the standard version of the HUI (4 weeks) and the standard version of the EuroQol-5D ('your health

today'); the second questionnaire includes the standard version of the HUI, but two slightly different versions of the EuroQol-5D. We have changed the 'today' health description to a 'bad day' health description and added a second 'good day' health description. Furthermore, patients are asked to indicate the average number of 'good' and 'bad' days per month and the number of days since their last 'bad' day with heavy bleeding. Patients are randomized to receive one of the two questionnaires. Furthermore, we have included sociodemographic questions in the questionnaire that cover age, gender, race, and education (i.e., what is the highest year or grade in school you completed?), items on out-of-pocket expenses, and time costs to estimate patient costs.

To estimate out-of-pocket expenses, patients are asked about their extra expenses due to the condition (such as clothes, underwear, bedlinen, furniture, tampons, pads). To estimate time costs, patients are asked about the number of days unable to go to work and/or unable to do their normal activities due to the condition.

Plan: All patients presenting to the Vincents' Gynecology Department at the Massachusetts General Hospital to seek treatment for menorrhagia are eligible for the study. These patients will be informed about the study and asked to participate. If these patients are able and willing to give informed consent they will be included in the study. In 1999, more than 300 patients with menorrhagia visited the Vincents' Gynecology Department. We estimate that approximately 150 consecutive patients will be approached for the study; assuming 70% participation, we anticipate that approximately 105 patients will complete the questionnaire.

Inclusion criteria: All consecutive patients presenting with menorrhagia visiting the Vincents' Gynecology Department at the MGH in order to seek treatment for their condition.

Exclusion criteria: Patients unable to give adequate informed consent. No further exclusion criteria exist.

Sample size: We hypothesize no substantial difference between the values obtained using the HUI and the EuroQol-5D (a linear relationship, slope=1, intercept=0). We developed our sample size based on the standard error of the intercept and slope. We derived these using the HUI data from the PI's previous work with 88 patients suffering from intermittent claudication. In this study the within-patient standard deviation of the HUI was 0.11. Using the observed between-patient distribution in the study as the distribution of the independent variable in our linear regression, we added normally distributed random errors [$N\{0, 0.11\}$] and simulated the results expected from our proposed study. These simulations indicate that to detect linearity between the HUI and EuroQol-5D scores, a sample size of 105 patients will give a standard error of the slope of 0.05 and a standard error of the intercept of 0.03.

Data Analysis

Upon data collections, descriptive statistics of the overall quality-of-life scores (i.e., means, standard deviations, medians, 95% confidence intervals) will be calculated and the most frequent response (mode) per attribute of the classification systems of both the HUI and EuroQol-5D will be reported. The results will be compared with published scores from women in the general population (age-matched). Multivariate and univariate regression analyses will be performed to investigate the relationship between the scores (linearity, slope=1, intercept=0) with time, age,

and other potentially influential variables as independent variables. Two-way analysis of variance will be performed to test the difference between the standard EuroQol-5D scores and the adjusted EuroQol-5D scores and to test for an order effect in the administration of the HUI and EuroQol-5D.

Specific Aim 2: To determine the relationship between the HUI and EuroQol-5D.

Progress: Specific Aim 2, or “Part 2” of the study, will be done after the data collected in part 1 have been analyzed.

Plan:

General population

A random representative sample of the general population will be recruited by random digit dialing. A professional survey firm will recruit the respondents and perform the interviews. The sample will be randomly divided into subgroups for the different mortality risks in the questions. The chosen mortality risks in the questions will cover the range between 0 and 100% mortality risk. For example, the following risks can be chosen for the subgroups: 0.5%, 1%, 2%, 5%, 10%, 15%, 25%, 50%, 75%, 99%. In our previous study, 1000 respondents were included, divided into 10 subgroups. The required sample size for the analysis, however, should be determined.

Interview: The interview will consist of the binary-gamble method and demographic questions. The estimated duration of the interview is 10 minutes.

In the binary-gamble method each person will be presented with a health vignette describing menorrhagia.

The health vignette presenting a woman with menorrhagia will be based on the health description found in the patient survey. The most frequent answer (mode) per attribute in the classification system of the HUI and EQ-5D will be reported and used to describe the health vignette. Before using the vignette in the population survey, the description will be discussed with medical experts and adjusted if necessary. After hearing the vignette, subjects will be asked to make a hypothetical choice between the certainty of remaining in the described health state versus undergoing a treatment with specified probabilities of attaining full health or immediate death (i.e., a binary-gamble question). The possible answers to the question are: “Yes, I will take the risk,” “No, I will not take the risk,” and “I don’t know.”

Previously, we included only one question with a single probability risk in the interview. Alternatively, we may consider including a second, follow-up question. This second question should be similar to the first, but would present a risk one level higher or lower, depending on whether the subject accepted or denied the treatment. This approach may be more powerful but may also introduce anchoring adjustment bias after the first question. The optimal design of the method remains to be determined.

Data analysis

From the binary-gamble method with one-question per respondent, non-parametric analysis and logistic regression analysis can be used to calculate the societal mean and median utility of a health state with menorrhagia. In the non-parametric approach, a distribution of responses is

constructed by calculating the proportion of yes-responses for each mortality risk. If the proportion of yes-responses is greater at the higher of two succeeding risks (which is illogical since the proportion choosing the treatment should decrease as the mortality risk increases), the responses are pooled for the two risk levels and the proportion is recalculated. Once the distribution curve is constructed, one obtains the empirical "survival-function" and the mean utility can be estimated by the area above the distribution curve (1 minus the area under the curve). The median utility corresponds to 1 minus the risk level (i.e., midpoint of a risk-interval) at which 50% would accept the bid according to the distribution curve. Multivariate logistic regression analysis is performed to assess the mean utilities parametrically. To estimate the parametric mean utility, the study sample means of the covariates can be included in the resulting regression models and the dependent variable will be plotted as a function of risk. The area above the curve represents the mean utility.

The calculated scores will be compared with the HUI and EuroQol-5D scores assessed in the patient survey. Furthermore, for validation purposes, we will add a second health description which was used in the previous study (i.e., amputation due to peripheral arterial occlusive disease). The results of the current study will be compared with the results from the previous study.

The binary-gamble method with two-gamble questions per respondent will yield censored data in a single-bounded interval and a double bounded interval, which allows other methods for data-analysis (e.g. based on Kristrom Spike Model, or Weibull model).

Specific Aim 3: Develop a cost-effectiveness model to evaluate minimally invasive treatments of menorrhagia.

Progress: A preliminary cost-effectiveness model of uterine artery embolization (UAE) compared with hysterectomy for patients with fibroids, which is the single largest cause of menorrhagia, has been developed. Using the best estimates for cost and effectiveness we found so far in this model, UAE had slightly lower mean cost and higher mean effectiveness than hysterectomy (\$3,975 and 22.66 QALYs compared to \$4,084 and 22.23 QALYs, respectively), making it a cost-saving alternative. This "base-case" analysis assumes that UAE has a low technical failure rate of only 2%, that it is effective in 90% of patients, and that fibroids recur in 0.1%. If the fibroids do not recur after successful embolization, then the mean cost decreases to \$3,877 and the mean effectiveness increases to 22.80 QALYs. If embolization is only effective in 75% of patients, then it is no longer cost saving, but the incremental cost-effectiveness ratio (ICER) is \$3,397/QALY.

This model, by necessity a simplification of reality, demonstrated minimal differences in costs and effectiveness between the two procedures. These results are likely to change after varying the assumptions about the costs and effectiveness of both procedures. We are currently refining the model and its assumptions.

Plan:

Model Development

A state transition (Markov) decision model will be developed in order to compare initial and long term benefits and costs of minimally invasive treatment strategies, such as cryoablation,

thermoablation, laser ablation, trans-cervical endometrial resection or ablation, radiofrequency ablation, and uterine artery embolization with the traditionally performed hysterectomy in patients with hemorrhagia. The model will contain a finite number of health states describing the consequences of possible clinical events. Secondary treatment and follow-up events will be built into the model. Transitions between each health state will be specified over a particular fixed time frame (i.e., cycles) by assigning different probabilities for each form of management under evaluation. The construct of the model will be based on literature and discussion with clinical experts.

The cost-effectiveness analysis will be performed according the guidelines of the US Panel on Cost-Effectiveness in Health and Medicine. In the analysis, we will estimate the total costs and effectiveness (in terms of quality-adjusted life years) of the initial procedures and events during follow-up. In addition, incremental cost-effectiveness ratios (additional costs divided by the effectiveness gained in comparison to the next best strategy) will be calculated. The cost-effectiveness analysis will be performed from the societal perspective. Sensitivity analyses will be performed by varying the effectiveness and costs estimates.

Data

Effectiveness: Quality-adjusted life years will be estimated for each treatment strategy on the basis of morbidity and mortality data, other clinical outcomes, and quality-of-life outcomes. Effectiveness data will mainly be retrieved from the literature and experts. Pre-treatment quality-of-life data will be collected from patients and the general public (the proposed study).

Costs: Costs incurred by the hospital and patients will be included in the model. Hospital costs of procedures and events in follow-up will be retrieved from the hospital accounting system (Transition Systems, Inc. TSI). In sensitivity analysis, we will use a range of costs retrieved by Medicare reimbursements for CPT-4 codes or DRG codes and the literature. Patient costs will include time costs and out-of-pocket expenses. Time costs will be estimated by multiplying the time expended for the intervention by the average wage for these women (Bureau of Labor Statistics). Out-of-pocket costs and time costs during follow-up will be estimated from the patient questionnaire and an ongoing study in the Department of Gynecology.

3.0 CLINICAL CHALLENGES

3.1 TRAUMA AND CRITICAL CARE

The Trauma and Critical Care Clinical Challenge is developing new, efficient technologies that reduce morbidity and mortality from trauma and critical illness. These developing technologies lessen: the time required for recovery, the pain and suffering associated with therapy, and the overall cost of patient care.

Task 1: Microsensors – Real-Time Blood Assay

Principal Investigator: Christopher Dube, PhD, Draper Laboratory, Cambridge, MA

The goal of the project is development of a microarray sensor technology that is capable of measuring a detailed signature profile of blood (or other body fluid) components in near real-time. Components under investigation include both soluble proteins and microbial pathogens. The project is driven by several needs: 1) ICUs need more detailed, timely information on the metabolic, inflammatory, or infectious state of a patient, 2) Near real-time serum level of indicator proteins (e.g. Parathyroid hormone (PTH) level during parathyroid surgery), and 3) Faster detection and identification of blood-borne infectious disease. In particular, the impact of development of the later is significant in that it would revolutionize diagnostic microbiology from current culture-based methods to faster, more precise, more sensitive technology. Through our collaboration with Dr. Stephen B. Calderwood, Chief of the Division of Infectious Disease at MGH, we have identified specific clinical applications of our sensor technology. These focus largely on detection and identification of blood-borne infectious disease. If successful, a direct-read, near real-time detection and identification of human pathogens will revolutionize diagnostic microbiology from largely culture-based methods to a detection/identification approach that is highly specific in its ability to discriminate pathogens with a technology platform than can provide sensitive measurements in a short period of time.

Key Results: The key milestones of the past year include: 1) Repeatable detection of the microbial pathogen *E. coli* O157:H7 using individually functionalized μ CANARY elements. In the previous quarter the CIMIT team demonstrated detection of *E. coli* O157:H7 using commercially available antibodies. This past year we have repeated *E. coli* O157:H7 detection and verified the detection sensitivity; 2) Demonstration of specific binding of *E. coli* O157:H7 to the anti-*E. coli* O157:H7 by showing a lack of binding of *E. coli* O157 knockout strain that does not express the O157 antigen. This was a very significant milestone because our detection relies on the specificity of the affinity coating for the target organism, and this was nicely demonstrated this past year; 3) Refinement of the molded PDMS microfluidic flow distributor and adoption of a SOP for detection of *E. coli*. The ability to disconnect the flow cell enables us to use the BioDot to functionalize the sensor elements as well and gives us improved hydrodynamic performance needed for optimal sensor performance. This type of flow cell is also key to incorporation of the μ CANARY sensor into a sensor system since this system requires that the sensor be replaced periodically. The projects final accomplishment (4) relates to the identification of peptide sequences that are specific to the three different *E. coli* variants under investigation. This work was done in conjunction with Prof. David Kaplan at Tufts University in the development of alternative affinity ligand reagents (ALRs) for the detection of microorganisms, based on peptides expressed on the outer surface coat of phage. These ALRs

will be used in conjunction with the μ CANARY sensors for detection of microbial pathogens. Although we have had very good results with our efforts to detect *E. coli* organisms, the team has been less successful with detection of DNA. This past year we began development of the μ CANARY sensor for DNA hybridization reactions. This involves attachment of biotinylated ssDNA to the μ CANARY surface, followed by detection of the complementary strand using the μ CANARY sensor. We were not able to detect the hybridization of the trial target sequences with the μ CANARY sensor, and so the team went back to developing a fluorescent assay (Rhodamine dye) to evaluate the attachment of the ssDNA to the surface, to be used in parallel with the μ CANARY sensor. The eventual application for DNA-based sensing is the identification of *E. coli* strains, based on the strain typing polymorphs developed by our MGH partner Dr. Stephen Calderwood and his group.

Specific Aim 1.: Determination of analytes of interest and detection requirements. To accomplish this Specific Aim the following items will be addressed:

- Characterize receptor coating application for microbial pathogens.
- Sensor system development.
- Sensor surface chemistry.
- Characterization of exposure to laboratory samples.
- Determine level of accuracy provided by technique.
- Exposure to fluid samples with unknown concentrations.
- Development of hardware.
- Development of software.

Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue Microsensor research under Cooperative Agreement No. DAMD17-02-2-0006.

Task 2: Application of Microwave Imaging to Rapid Non-Invasive Detection of Intracranial Hematoma

Principal Investigator: *Lt Col Geoffrey S. F. Ling, MD, PhD, Uniformed Services University of the Health Sciences, (USUHS), Bethesda, Maryland*

Trauma care has advanced remarkably over the past 20 years. A leading contributor is the introduction of treatment algorithms taught in Advanced Trauma Life Support (ATLS) and Advanced Cardiac Life Support (ACLS) courses. In practice, to use these algorithms, medical providers must have adequate training and appropriate diagnostic tools. It is the lack of both that has prevented military first providers (combat medics) from meeting this standard of care.

The Radio Frequency Triage System (RaFTS) unit is a handheld device facilitating the diagnosis of severe combat injuries directly on the far-forward battlefield. The prototype concept utilizes the detection of the physical modulation of radio frequencies by living tissue to transmit or backscatter radio frequencies based on the physical dielectric constant inherent in different tissues. This device will provide combat medics with patient vital signs, electrocardiogram

(EKG), percent blood oxygenation and ability to diagnose common occult trauma conditions, e.g., intracranial hemorrhage and pneumothorax.

Specific Aim 1: To demonstrate the feasibility of applying the microwave diagnostic tool to accomplish the following:

- to identify pneumothorax,
- to identify the presence of blood in the epidural space,
- to identify compartment syndrome,
- to detect intraventricular hematoma, and
- to detect intraparenchymal hematoma.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To perform additional *in vivo* studies of pneumothorax and compartment syndrome in pigs using the RAFTS system.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3: Using RAFTS, perform baseline studies in normal human volunteers to determine the RF signals under normal uninjured conditions:

- Determine baseline signature of the head,
- Determine the baseline signature of the chest,
- Determine the baseline signature of the leg, and
- Characterize RAFTS signal response to blood, bone and bone-blood interface.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue this research under Cooperative Agreement No. DAMD17-02-2-0006

Task 3: Near-Infrared Reflectance Spectroscopy (NIRS) to Assess Regional Ischemia both during Trauma Resuscitation and at the Bedside in the Intensive Care Unit

Principal Investigator: Juan Carlos Puyana, MD, University of Pittsburgh Medical Center

The overall objective of this research effort is to use Near-Infrared Reflectance Spectroscopy (NIRS) and other new minimally invasive technologies to determine the severity and reversibility of hemorrhagic shock by means of assessing organ specific cellular function and metabolism.

Presently the team is focusing on establishing the effects of spontaneous breathing on tissue blood gases. Previous experiments so far have shown that the PCO₂ of the muscle correlates well with the severity of shock. However these data has not been obtained in shocked animals without ventilatory support and without controlling for ventilation and arterial CO₂.

The work completed so far has allowed us to show that the use of a multi-parameter sensor facilitates the identification of a specific organ response to hemorrhage. That changes in baseline tissue PCO₂, PO₂ and pH occur promptly after hemorrhage and that these responses are similar in all organs studied (liver, gut peripheral muscle, and stomach). Also, the team has demonstrated that changes in tissue pH and PCO₂ in peripheral muscle correlate well with severity of blood volume lost and with the resuscitative interventions used to replace hypovolemia.

Key Results: Validation studies at the University of Pittsburgh Medical Center will begin once all animal use approvals have been granted.

Specific Aim 1: To develop minimally invasive techniques to measure peripheral organs (Bladder) pH in the victim of hemorrhagic shock and evaluate the potential of this method as a predictor of multiple organ dysfunction syndrome (MODS) and a guide for resuscitation.

Progress: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Plan: Project completed. See Annual Progress Report October 1, 2000 through September 30, 2001.

Specific Aim 2: Validation of NIR for tissue pH measurement

Progress: Validation studies at the University of Pittsburgh Medical Center will begin once all animal use approvals have been granted.

Plan: To initiate validation studies.

Task 4: Noise-Enhanced Tactile Sensation for the Management of Sensory Deficits in Patients with Stroke

Principal Investigator: D. Casey Kerrigan, MD, Spaulding Rehabilitation Hospital (SRH), Boston, MA

The overall goal of this research is to gain an increased understanding of how noise affects the detection and discrimination of mechanical cutaneous stimuli in subjects with impaired sensation, and also to establish a scientific foundation for the development of a clinically useful noise-based technique for improving tactile sensation in humans.

Key Results: Twenty-one subjects were screened for the project which included a mental status examination and a comprehensive battery of sensory tests of both hands. Sensory tests included light touch with monofilaments, hot-cold and 2 point discrimination, proprioception and muscle strength testing. It was demonstrated that electrical noise can, in fact, slightly enhance the ability of patients with stroke to detect subthreshold mechanical stimuli.

Specific Aim 1: Design and construct a suitable apparatus for patient experiments.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: Demonstrate the feasibility of both the apparatus and an experimental protocol through implementation in patients with stroke; collect data on patients with stroke.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001

Specific Aim 3: Analyze data to test the hypothesis that electrical noise can enhance the ability of patients with stroke to detect subthreshold mechanical stimuli.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

3.2 VULNERABLE PLAQUE PROGRAM

Task 1: Vulnerable Plaque Detection and Treatment

Principal Investigator: James E. Muller, MD and Thomas J. Brady, MD, MGH

Key Results: Vulnerable Plaque Program continued to meet its goals and establish new ones. The main activity of the Program continues to be the scientific projects (see below for project reports). Leadership of the Program continues to address thematic, administrative and support issues in an attempt to enhance the overall quality and scope of the Program. The following represents the programmatic accomplishments during the past quarter.

Specific Aim 1: Establish a Vulnerable Plaque Lecture Series.

Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue Vulnerable Plaque research under Cooperative Agreement No. DAMD17-02-2-0006.

Task 2: Detection of Vulnerable Plaque using Optical Coherence Tomography

Principal Investigator: Brett Bouma, PhD, MGH

The specific goal of this research was to apply optical coherence tomography (OCT) for monitoring plaque development and response to systemic therapy in an animal model for atherosclerosis. Prior to this work, no longitudinal studies have been conducted within individual animals. The advantage of OCT is that cross-sectional images with a resolution approaching that of histopathology can be obtained *in vivo* (without sacrifice) so that disease can be monitored over time in individual animals. In order to make longitudinal studies with OCT practical, several technical issues have been addressed including imaging in the presence of blood, avoiding motion artifacts and providing sufficient resolution for plaque characterization.

Atherosclerotic disease in rabbits was generated using a high-cholesterol diet and focal balloon injury in the aorta and iliac arteries. The goal of the study was to monitor plaque response to diet modification and systemic therapy. Balloon injury was performed at the initiation of high-cholesterol diet. The first imaging time point was at 4 months. At that time, the rabbits were divided into separate arms of the study including diet modification and systemic therapy. The final imaging time point was intended to identify plaque response. The primary technical challenges addressed in this work were associated with the *in vivo* imaging. Balloon injury was performed using femoral access. OCT images of the rabbit iliac arteries and aorta were obtained by insertion of the imaging catheter through the carotid artery.

A second goal of the research was to investigate the ability of OCT to characterize plaque composition. As there is no existing gold standard for plaque characterization *in vivo*, the team has conducted an extensive *in vitro* study.

Key Results: The team has advanced the capabilities of OCT for imaging *in vivo* by resolving three key technical issues. First, the team has developed methods for displacing blood from the iliac and aorta using balloon occlusion and saline flush. Second, the team has demonstrated a sufficient image acquisition rate to avoid motion artifact due to respiration and pulsatile blood flow. Finally, the team has demonstrated that characteristic features in plaques can be resolved using a catheter that provides a resolution of approximately 10 microns.

The team has demonstrated that OCT imaging of the rabbit iliac and distal aorta can be performed in live animals without sacrifice. The images have demonstrated that OCT provides adequate resolution and contrast to identify focal lipid rich plaques and that the extent of disease can be quantified. At the first OCT imaging time point the team has uncovered two problems suggesting that the time scale of our study must be extended. First, the young age of the rabbits acquired for the study results in small vessel sizes. This has made vessel ligation a challenging problem following imaging. Failure to adequately ligate the carotid has resulted in the death of three rabbits. A second problem is that the frequency of observing localized lipid rich plaques in the iliac and distal aorta is less than anticipated based on our preliminary studies. Extending the timeframe of the study should lessen the impact of both of these problems. The team is therefore requesting a no-cost extension for a period of six months so that both imaging time points can be delayed in all remaining rabbits.

Specific Aim 1: To develop, optimize and apply OCT imaging for the detection of vulnerable atherosclerotic plaques. To accomplish this Specific Aim the following items will be addressed:

- To identify OCT morphologic features that distinguish vulnerable from stable plaques,
- To determine catheter and imaging characteristics in a porcine model, and
- Validation of a rabbit atherosclerosis model.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: To continue Vulnerable Plaque research under Cooperative Agreement No. DAMD17-02-2-0006.

3.3 STROKE

Stroke is the third leading cause of death and a major disability for over 4 million stroke survivors in the United States. There are 700,000 new stroke cases every year. Stroke has an economic impact of \$30 billion a year.

The Acute Stroke Program at Partners HealthCare System has offered immediate evaluation and advanced emergency treatment over the last decade. Construction of a specially designed angiographic suite, which includes both state of the art MRI and digital subtraction angiographic (DSA) instruments, is nearing completion at the MGH and is expected to be operational by the spring of 2001. This MRI/DSA unit will enable physicians to optimize delivery of existing stroke treatments, and, at the same time, provide CIMIT investigators with access to this facility for the rapid advancement of novel therapies in the management of acute stroke.

The overall goals of the CIMIT Stroke Program are: 1) to protect the brain from ischemic brain injury with brain hypothermia, 2) to treat clots that obstruct brain blood flow before they cause permanent brain injury; 3) to develop better means of non-invasively monitoring the brain for dangerously low blood flow and brain hemorrhage, 4) to develop non-human primate models to predict brain injury, and 5) to provide technology assessment to evaluate new therapies for the treatment of stroke.

Task 1: Acute Stroke Management – Neuro-Protection

Principal Investigator: Walter J. Koroshetz, MD, MGH and Albert S. Lee, MD, MGH

Brain cooling is the most potent neuroprotective strategy in the management of acute stroke. Its use as a neuroprotectant in ischemic brain injury is limited only by the lack of the means to achieve cerebral hypothermia in a rapid, safe fashion. Ongoing CIMIT funded research is focused on the development of novel interventional modalities to selectively cool the surface of the cerebral cortex to provide neuroprotection for stroke patients.

Specific Aim 1: Develop a means to quickly cool the brain cortex to afford neuroprotection.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Task 2: MRI Guided Rapid Laser Endovascular Photoacoustic Recanalization (LEPAR) for Hyperacute Stroke and Stroke Predictive Modeling

Principal Investigator: R. Gilberto Gonzalez, MD, PhD, MGH

The emphasis of this project remains the same as for the previous year. In the last year the team has been working in two main areas on this project: experiments with the arterial bypass device to supply blood to ischemic brain regions via the microcatheter (a potential therapeutic approach

for human stroke as well) and experiments with the survival macaque stroke model (needed to assess the longer term effect of potential therapies as well as to obtain control MRI data on stroke evolution in this new model). The arterial bypass device was improved via more bench top experiments and the purchase of a dual channel ultrasonic flow meter, allowing us to measure two flow streams at once (i.e. arterial blood and a second flow of dilutant solution, e.g. saline, or other solution mixed into the blood stream). Additional *in vivo* experiments utilizing this setup were partially successful.

The second focus area has been the survival macaque stroke model. So far the team has recovered one animal following the acute stroke procedures. This animal was recovered after 60 minutes of MCA occlusion, and was survived successfully for 24 hours. Observations at 24hrs after stroke induction showed that the animal appeared healthy with no noticeable deficits. This is an important advance as it demonstrates successful recovery from acute stroke, which is necessary for the long terms plans for this stroke model.

Key Results: Four animals were studied with the bypass setup: in two animals the correct flow rate was achieved and brain tissue in the lesion area was maintained viable for 60-90 minutes, while in one animal the flow rate was too low and the lesion tissue infarcted, while in one animal the flow rate was too high and hemorrhage resulted. These results identify the future directions for this part of the project: to improve flow stability using a better blood pump and to improve the means of obtaining the correct flow rate in each animal by measuring or calculating accurately the fluid pressure at the tip of the microcatheter within the brain.

Specific Aim 1: To demonstrate efficacy and tissue safety of the LEPAR device and to maximize patient safety by defining the irreversible brain injury probability by diffusion MRI in a primate model.

Progress: Project completed. See Annual Progress Report, October 1, 2000 to September 30, 2001.

Plan: Project completed. See Annual Progress Report, October 1, 2000 to September 30, 2001.

Task 3: Optical Monitoring and Imaging of Stroke

Principal Investigator: *Walter J. Koroshetz, MD, MGH and David A. Boas, PhD, MGH*

Note: We will be forwarding written correspondence regarding our intention to withdraw this study.

The ischemic brain injury (stroke) program is targeted at developing better means of non-invasively monitoring brain for dangerously low blood flow and for brain hemorrhage; treating clots that obstruct brain blood flow before they cause permanent brain injury; protecting brain from ischemic brain injury with brain hypothermia. The optical imaging project is focused on developing a new bedside capable imaging modality for continuous quantitative monitoring of cerebral perfusion and oximetry.

Key Results: During the last quarter significant progress was made in diffuse optical technology for characterizing layered media. This technology is central to cerebral oximetry in which the layered structure of scalp, skull and brain must be characterized. The key developments include: 1) New time resolve near infrared spectroscopy instrumentation for improved optical property determination, 2) time resolved Monte-Carlo modeling of layered media and 3) composing and submitting a Human protocol for cerebral oximetry measurements on healthy people.

Specific Aim 1: To finish the construction and testing of the 3rd generation CW instrument and the 1st generation RF instrument.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Specific Aim 2: Develop quantitative 3D reconstruction algorithms.

Progress: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Plan: Project completed. See Quarterly Progress Report September 30, 2001 through December 31, 2001.

Specific Aim 3: To cross-validate the sensitivity and quantitative accuracy of the optical measurements with structural and functional information obtained with MRI, and to obtain preliminary results for "spin-off" projects.

Progress: No activity this quarter.

Plan: Once DoD animal use approval is received, piglet measurements will be initiated. The piglet data will provide preliminary feed back to complete instrument.

Specific Aim 4: Establish feasibility of translating technology to humans.

Progress: Toward this Specific Aim an IRB protocol entitled "Continuous Monitoring of Cerebral Hemoglobin Oxygenation Using a Hybrid Time-Domain/Continuous-Wave Diffuse Optical Tomography System." (Accession #2001P 001632) was composed and submitted.

Plan: Depending on progress with approval this study of healthy humans will be started. Also, preparation will begin for a subsequent protocol to look at chronic patients with head trauma.

Task 4: Neuronal Injury and Neuroprotection in Epilepsy: Proton Beam Radiation for Intractable Epilepsy

Principal Investigator: Jonathan L. Brisman, MD, MGH

A new model of proton beam radiosurgery (stereotactically focused irradiation) of the rat hippocampus has been developed. This model appears to be robust with brain necrosis evidenced reliably after a 3 month latency using doses of 90 Cobalt Gray Equivalents (CGE) or greater. This unilateral necrosis has been shown to correlate with increased T2 signal on MRI, decreased ability to perform the Morris Water Maze and the diminution of excitatory post-synaptic potentials and granule cell field spike obtained using *in vivo* microelectrode recordings. Positive alterations in heat shock protein, parvalbumin, calbindin and calmodulin have been detected. Upregulation of heat shock protein at non-necrotic doses may be important in explaining why low-dose irradiation reduces seizure activity in humans. These findings have been presented orally at the Congress of Neurological Surgeons Annual Meeting, September 2000, at the Spring Hippocampal Research Conference in spring 2000 and presented at the national Radiology Conference in fall 2000.

Two additional time points after irradiation have been employed to further study the time course of irradiation effects on the rat brain. Twelve animals have been studied five hours after irradiation and eighteen animals ten months after irradiation. The animals studied at the five hour point show apoptotic cell death in the irradiated hippocampus in a dose-dependent fashion. The ten month animals appear to show physiologic changes even at the lower doses used; histologic analysis has not yet been done.

A cohort of 40 animals has been irradiated after receiving pilocarpine status epilepticus. These animals have been analyzed physiologically and their brains stained for histologic and immunochemical analysis. In addition to the immunochemistry previously used in the normal rat brain irradiation study, a "Timm Stain," that typically shows axonal sprouting after pilocarpine seizures, was employed to determine whether irradiation has any effect on this neuronal response to status epilepticus. Preliminary results suggest that the pattern is altered with the higher doses employed.

Specific Aim 1: To characterize the histologic and electrophysiologic effects of proton beam irradiation in the normal rat brain.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: To determine whether proton beam radiation can alter the neurophysiology or anatomic changes in animals that have undergone 24 hours of perforant pathway stimulation.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 3: To determine the brain MRI appearance of rodents subjected to varying dosages of proton beam irradiation as well as rodents that have undergone 24 hours of perforant pathway stimulation.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Task 5: Measurement of Vascular Reactivity by Functional MRI in Cerebral Amyloid Angiopathy

Principal Investigator: *Steven M. Greenberg, M.D., Ph.D.*

In cerebral amyloid angiopathy (CAA), the β -amyloid peptide is deposited in small and medium-sized vessels of the leptomeninges and cerebral cortex. Amyloid replaces vascular smooth muscle, transforming vessels into rigid structures. In severe cases, this leads to rupture of the vessel wall and cerebral hemorrhage. Current diagnostic methods for CAA are limited to pathologic examination of the brain or radiographic demonstration of multiple hemorrhages in a characteristic distribution. Although CAA often affects a large number of cerebral vessels, whether the disease changes the flow characteristics of these vessels is unknown. Functional MRI (fMRI) can reliably assess human cerebral oxygenation, blood flow, and, with gadolinium injection, cerebral blood volume. We are investigating two stimuli that reliably increase cerebral blood flow in humans: visual stimulation using a flashing checkerboard pattern and CO₂ inhalation. Because cerebral blood flow is intimately tied to oxygen demand, visual stimulation increases flow through the normal activation of neuronal activity, and the recording of such changes has been the cornerstone of fMRI. By increasing CO₂ in the blood, CO₂ inhalation results in dilation of cerebral vessels and increased cerebral perfusion. We hypothesize that changes in blood vessels secondary to amyloid deposition alter the degree to which vascular tone can respond to both increased neuronal activity and CO₂ inhalation. This project investigates whether fMRI can document a difference in the response of cerebrovascular tone to these two stimuli between patients and controls. These techniques may enable us not only to diagnose cerebral amyloid angiopathy before the first hemorrhagic stroke, but also to follow patients over time, assessing the progress of their disease and response to potential therapies.

Key Results: Thus far, 4 control subjects and two CAA subjects have been studied using fMRI. Data analysis revealed a robust response in blood flow to both visual stimulation and CO₂ inhalation in the control subjects, although we have not detected any quantitative differences between CAA subjects and controls with this limited sample size. We are eager to investigate whether this observation is true in other CAA subjects.

Specific Aim 1: To develop a protocol for measuring cerebrovascular dilation in response to visual stimulation and 5% CO₂ inhalation in the elderly.

Progress: Cerebrovascular reactivity to visual stimulation has been measured in 4 control subjects by examining the changes in blood oxygen level dependent (BOLD) signal and regional cerebral blood flow. MRI revealed increased regional cerebral blood flow responses to visual stimulation (Figure 1) in 3 patients and CO₂ inhalation in 2 subjects (Figure 2). Two subjects were not administered CO₂ and a fourth subject, in whom no blood flow response was measured during visual stimulation, likely closed her eyes during much of the MRI.

One additional CAA subject was scanned this quarter, but did not undergo CO₂ inhalation during the study. We are eager to investigate whether this difference can be detected in additional CAA subjects.

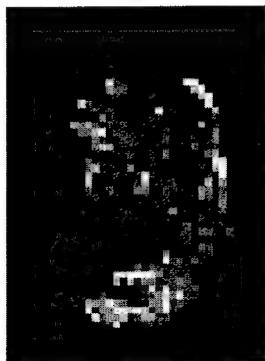


Figure 1. (WN) BOLD sequence from a 68-year-old control patient exposed to a visual stimulus. Areas colored red and orange demonstrate increased regional cerebral blood flow.

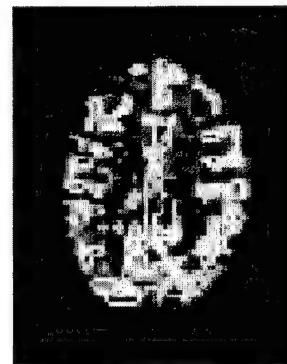


Figure 2. (FS) BOLD sequence from a 67-year-old control subject exposed to 5% CO₂ demonstrates more diffusely distributed changes in regional cerebral blood flow when compared to the BOLD response obtained with visual stimulation.

Plan: An additional control subject and three additional subjects with CAA will be studied.

4.0 TECHNOLOGY ASSESSMENT AND OUTCOMES ANALYSIS PROGRAM***Principal Investigator: G. Scott Gazelle, MD, MPH, PhD***

The Technology Assessment and Outcomes Analysis Program represents an evolution of the Program established three years ago with the support and guidance of CIMIT leadership. As a result of discussions with members of the Operations Group, and in view of changes in CIMIT over the years, we have reshaped the Program to concentrate our research efforts on two major focus areas. Service, policy and administrative components of the Program are now concentrated in a Program Core. The Technology Assessment and Outcomes Analysis Program will be an important component of ongoing CIMIT technology development efforts. The Program will help CIMIT focus resource allocation for the development of innovative technologies that can result in improved patient care; perform studies to assess the effectiveness, cost and cost-effectiveness of technologies under development; and demonstrate the value of these technologies to the public, physicians, payers, industry, and legislators in order to facilitate appropriate clinical implementation. Our overall goal is to help CIMIT determine and optimize the outcomes of its research efforts, and more generally to redefine the manner in which healthcare interventions are valued.

The Technology Assessment and Outcomes Analysis Program is divided into a Core and two major Outcomes Projects. The Program Core functions to: 1) assist the Operations Group with resource allocation decisions by performing preliminary analysis of technologies identified in requests for funding; 2) provide scientific direction, project coordination and administrative support to two major Outcomes Research Projects; and 3) provide consultation and guidance to CIMIT investigators and collaborators regarding issues such as project feasibility, study design, optimal endpoint determination and data analytic or statistical methods.

The two Outcomes Projects were developed in response to the needs of CIMIT major focus areas and are the result of ongoing collaborations. The models developed and research results from each of these projects are expected to be resources not only for CIMIT, but also for collaborators in government and industry.

TECHNOLOGY ASSESSMENT PROGRAM CORE

Within the larger Technology Assessment and Outcomes Analysis Program, the Program Core supports CIMIT research, administrative and clinical activities using a variety of analytic techniques to investigate specific technology related questions as well as broader national health policy issues. Projects may range from examining the potential cost-effectiveness of a new technology under consideration for CIMIT funding, to determining the optimal point of intervention in any one of a number of broad disease areas.

The Program Core is fully integrated with the entire spectrum of CIMIT research, clinical, educational and administrative activities. Its primary activities are the development and application of rigorous analytic methodologies including clinical epidemiology, cost-effectiveness analysis, decision analysis, economic analysis and risk analysis. The Program provides the infrastructure and expertise to properly evaluate new medical technologies at all stages of development, and in so doing, to promote the optimal use of increasingly limited health care resources. With CIMIT support and guidance, the team has succeeded in establishing a large and capable group of investigators. These investigators have developed a rich network of collaborations throughout CIMIT. We have collaborated and/or consulted with other CIMIT

investigators on issues such as project feasibility, study design, endpoint determination, and approaches to data analysis. We have also assisted with primary data collection and analysis. This work complements other more traditional laboratory and/or clinical research being carried out by individual CIMIT investigators or within the context of major CIMIT Programs.

Moving forward, the Program Core will continue to support the entire CIMIT scientific and administrative community, as well as the two Technology Assessment and Outcomes Analysis Program Research Projects (i.e., the Vulnerable Plaque and Operating Room of the Future Outcomes Projects). The Program Core will help CIMIT focus resource allocation for the development of innovative medical technologies that can result in improved patient care; provide advice on and perform studies to assess the effectiveness, cost and cost-effectiveness of new technologies under development; and demonstrate the value of these new technologies to the public, physicians, payers, industry, and legislators so as to facilitate their appropriate dissemination and implementation.

Specific Aim 1: The CIMIT Operations Group with resource allocation decisions via preliminary analysis of technologies identified in requests for funding.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 2: Provide scientific direction, project coordination and administrative support to major Technology Assessment Program Research Projects.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 3: Provide consultation and guidance to CIMIT investigators and collaborators regarding issues such as project feasibility, study design, optimal endpoint determination and data analytic or statistical methods.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 1: Develop, refine and verify a comprehensive model of cardiovascular disease and therapy, focusing on the role of "vulnerable plaque".

A primary aim of the Vulnerable Plaque Outcomes Project is to develop a comprehensive model of cardiovascular disease and therapy which can be used to evaluate the full spectrum of

potential diagnostic and therapeutic interventions, from the identification of high-risk individuals, through non-invasive and catheter-based diagnostic testing, to the delivery of local and/or systemic therapy. In the next two years, the team will build a decision model and use it to investigate a number of clinical and policy issues which face those developing, using, or funding these interventions.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

OPERATING ROOM OF THE FUTURE OUTCOMES PROJECT

The overall aim of the Operating Room of the Future (ORF) project is to develop new surgical equipment, procedures and processes that will result in improved patient outcomes, operating room efficiency, or both. The ORF project has sought to establish links to both industry partners and academic researchers who are developing these new technologies, in order to make the ORF surgical suite a comprehensive test platform for product and process development. Substantial progress has already been made towards creating a prototype operating room which incorporates modular equipment, new surgical information systems, and new approaches to process flow. Testing the effects of each of these components on system efficiency, cost, or cost-effectiveness is complex and time-consuming and expensive. Since it is impossible to perform a truly randomized controlled trial in the surgical environment, the team has developed a factorial study design to introduce and evaluate new technologies in a staged process. To help understand how individual technologies and innovations contribute to changes in outcomes and to identify new opportunities for new technologies and innovations, the team developed a discrete event computer simulation model. This allows us to simulate both the current surgical system and proposed changes. In the OR of the Future Outcomes Project, the team will continually develop and utilize this model in order to evaluate this complex and changing system. These models and stage trials will focus on identifying the most effective new technologies and techniques as they are developed, and thus help to guide resource allocation for further development and clinical implementation.

It is important to note that the CIMIT Operations Committee requested that work on this project be limited entirely to the OR efficiency studies originally described in relation to the PinPoint tracking system in our initial proposal. We therefore agreed to limit our research activities accordingly (focusing, however on a similar system made by Sentinel Technology), and have scaled back on the effort committed to the project. Work on other components of the original proposal which is requested by program leaders in this area will require additional funding, commensurate with the magnitude to the work to be done.

Specific Aim 1: Develop a discrete event simulation model for the ORF Surgical Suite.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 2: Evaluate surgical technologies and processes as they are integrated into the ORF.

Progress: Project completed. See Quarterly Progress Report, October 1, 2001 through December 31, 2001.

Plan: To continue our efforts in Technology Assessment under Cooperative Agreement No. DAMD17-02-2-0006.

5.0 REFERENCES

Akinc AB, **Langer R.** Measuring the pH Environment of DNA Delivered Using Nonviral Vectors: Implications for Lysosomal Trafficking. *Biotechnology and Bioengineering*. 2002, 78, 503-508.

Baim D, Brady TJ, Casscells SW, Dunne M, Fuster V, **Muller JE**, Tearney G, Wasserman B. Thoughts on the role of the healing professions and the events of September 11, 2001. *Circulation* 105(12):1509-10, 2002.

Bauer JJ, Magee JH, Moses G, Leitch R, **Dawson SL**. Medical simulation training initiative (MSTI), SPIE Conference on Battlefield Biomedical Technologies, v.4037, in press, 2002.

Ben-Ur E, **Salisbury K.** A 5 F haptics device for laparoscopic surgery simulation. SPIE Conference on Battlefield Biomedical Technologies, v.4037, in press, 2002.

Boas DA, Gaudette T, Strangman G, Cheng X, Marota JJ, Mandeville JB. The accuracy of near infrared spectroscopy and imaging during focal changes in cerebral hemodynamics. *Neuroimage* 13(1):76-90, 2001.

Boas DA, Gaudette TJ, Arridge SR. Simultaneous imaging and optode calibration with diffuse optical tomography. *Optics Express* 8:263, 2001.

Cingo NA, Soller BR, **Puyana JC**. Multivariate calibration modeling of liver oxygen saturation using near-infrared spectroscopy. *Proc SPIE*, 3911, in press, 2002.

Cotin SC, **Dawson SL**. CAML: a general framework for the development of medical simulation systems. SPIE Conference on Battlefield Biomedical Technologies, v.4037, in press, 2002.

Cramer S, **Koroshetz WJ**, Schwamm L, Buonanno F, Rordorf G. Predictors of mortality in stroke patients admitted to an intensive care unit. *Critical Care Medicine* (in press) 2002.

Cunningham BT, Regan R, Weinberg M, Clapp C, Hildebrant E, Williams J. Miniature silicon biological assay chip and applications for rapid battlefield diagnostics. *Proc Aerospace Sympos* (in press) 2002.

Dawson SL, Cotin S, Meglan D, Shaffer DW, Ferrell MA. Designing a computer-based simulator for interventional cardiology training. *Catheter Cardiovasc Interv*. 51(4):522-7, 2001.

Franco RA Jr, **Zeitels SM**, Farinelli WA, Anderson RR. 585-nm pulsed dye laser treatment of glottal Papillomatosis. *Ann Otol Rhinol Laryngol* 111(6): 486-492, 2002.

Garcia-Cardena G, Comander J, Anderson KR, Blackman BR, **Gimbrone MA**. Biomechanical activation of vascular endothelium as a determinant of its functional phenotype. *Proc Natl Acad Sci* 98(8):4478-85, 2001.

Gleason S, Furie KL, Ley MH, O'Donnell J, McMahon PM, Beinfeld MT, Halpern E, Mullins M, Harris G, Koroshetz WJ, **Gazelle GS**. Potential influence of acute CT on inpatient costs in patients with ischemic stroke. *Acad Radiol* 8(10):955-64, 2001.

Greenberg SM. Cerebral amyloid angiopathy and vessel dysfunction. *Cerebrovasc Dis* 13 Suppl 2:42-47, 2002.

Greenberg SM. First international conference on cerebral amyloid angiopathy, October 5-6, 2000, Boston, MA. *Amyloid* 8(2):143-146, 2001.

Grikscheit TC, **Vacanti JP**. The history and current status of tissue engineering: The future of pediatric surgery. *J Pediatr Surg* 37(3):277-288, 2002.

Hirosue S, Muller BG, Mulligan RC, **Langer R**. Plasmid DNA encapsulation and release from solvent diffusion nanospheres. *J Control Release* 70(1-2):231-242, 2001.

Ilic L, Gowrishankar TR, Vaughan TE, Herndon TO, **Weaver JC**. Microfabrication of individual 200 microm diameter transdermal microconduits using high voltage pulsing in salicylic acid and benzoic acid. *J Invest Dermatol* 116(1):40-49, 2001.

Izumrudov VA, Zelikin AN, Putnam D, Shastri P, **Langer R**. Aliphatic ionenes as gene delivery agents: elucidation of structure-function relationship through modification of charge density and polymer length. *Bioconjugate Chemistry*, in press, 2002.

Kaban LB. Biomedical technology revolution: opportunities and challenges for oral and maxillofacial surgeons. *Int J Oral Maxillofac Surg* 31(1):1-12, 2002.

Lorenzo HK, Teixeira J, Pahlavan N, Laurich VM, Donohoe PK, **MacLaughlin DT**. New approaches for high-yield purification of Mullerian inhibiting substance improve its bioactivity. *J Chromatogr B Biomed Sci Appl* 5;766(1):89-98, 2002.

Lowe HC, **Oesterle SN**, Burkhoff D. Alternatives to traditional coronary bypass surgery. *Semin Thorac Cardiovasc Surg* 14(1):110-118, 2002.

Lynn DM, **Langer RJ**. Degradable Poly(β -Amino Esters): synthesis, characterization, and self-assembly with plasmid DNA. Amer Chem Soc, in press, 2002.

McDannold N, King RL, **Jolesz FA**, Hynynen K. The use of quantitative temperature images to predict the optimal power for focused ultrasound surgery: *in vivo* verification in rabbit muscle and brain. *Med Phys* 29(3):356-365, 2002.

Meiler SE, Hung RR, Gerszten RE, Gianetti J, Li L, Matsui T, **Gimbrone MA**, Rosenzweig A. Endothelial IKK beta Signaling is Required for Monocyte Adhesion under Laminar Flow Conditions. *J Mol Cell Cardiol* 34(3):349-359, 2002.

Nasseri BA, Vacanti JP. Tissue engineering in the 21st century. *Surg Technol Int.* 10:25-37, 2002.

Ottensmeyer M, Salisbury K. *In vivo* mechanical tissue property measurement for improved simulations. Submitted for publication, 2002.

Ottensmeyer M, Salisbury K. TEMPEST, a tissue measurement tool. SPIE Conference on Battlefield Biomedical Technologies, v.4037, in press, 2002.

Putnam D, Locher C, Langer R. Nanoparticle Adjuvancy of a HIV-*env*GP120 Epitope DNA Vaccine. Submitted for publication, 2002.

Putnam D, Zelikin AN, Izumrudov VA, Langer R. Poly-histidine-PEG:DNA nanocomposites for gene delivery. Submitted for publication, 2002.

Shaffer DW, Dawson SL, Muller J. Current Perspective: Design principles for the use of simulation as an aid in interventional cardiology training. Submitted for publication, 2002.

Smith JJ, Henderson, JA, Baim DS. The FDA and Reprocessing of Single-Use Medical Devices: A Revised Policy and New Questions. Submitted for publication, 2002.

Sodian R, Hoerstrup SP, Sperling JS, Daebritz S, Martin DP, Schoen FJ, Vacanti JP, Mayer JE. Tissue engineering of heart valves: *in vitro* formation of viable tissue. *J Heart Valve Disease*, in press, 2002.

Soller BR, Cingo N, Puyana JC, Khan T, Hsi C, Favreau, J, Heard SO. Regional hepatic dysoxia during hemorrhagic shock in swine. Submitted for publication, 2002.

Young CS, Terada S, Vacanti JP, Honda M, Bartlett JD, Yelick PC. Tissue engineering of complex tooth structures on biodegradable polymer scaffolds. *J Dent Res* 81(10):695-700, 2002.

Zelikin AN, Lynn DM, Farhadi J, Martin I, Shastri V, Langer R. Erodible conducting polymers for potential biomedical applications. *Agnew Chem Int Ed* 41:141-144, 2002.

6.0 APPENDICES

APPENDIX A: CIMIT EDUCATION PROGRAM

Program Director: Reuben Saul Mezrich, MD, PhD, BWH

The Education Program was established to develop innovative methods of training and education in technology-based and interdisciplinary medical research and practice. The intent was to develop a program that would create novel approaches to training and education, integrated with all of CIMIT's research and clinical activities. The Program's principal activities in the past quarter included the development of simulation-based training tools, oversight of CIMIT's internal education Forum, and the integration of students into CIMIT's research activities. These activities were carried out in order to help CIMIT with the Specific Aims, below. Aspects of the Education Program, devoted to the Simulation Program and the Surgical Planning Lab, will be directly incorporated into these programs. Forum activities will continue as before, with greater emphasis on technology directed to medical care, in order to reflect a heightened interest in creating more technology/medical interactions.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Specific Aim 2: Engage students in CIMIT research on a regular and formal basis.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue work in this area under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 3: Develop interdisciplinary forums for the exchanges of ideas.

Progress: Project completed. See Quarterly Progress Report October 1, 2001 through December 31, 2001.

Plan: To continue the CIMIT Forum under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 4: Develop innovative, technology-based outreach programs.

Progress: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

Plan: Project completed. See Quarterly Progress Report January 1, 2001 through March 31, 2001.

APPENDIX B: CIMIT Regulatory Affairs Initiative***Program Director: John J. Smith, MD, JD, MGH***

Maximum clinical impact of safe and effective new medical technologies is heavily dependent on timely Food and Drug Administration (FDA) marketing approval and third-party payer coverage/reimbursement. The Regulatory Affairs Program at CIMIT provides a unique, national resource to address regulatory and coverage/reimbursement challenges throughout the product development lifecycle.

During this quarter, the Regulatory Affairs Program continued its efforts to make the existing regulatory and coverage/reimbursement system more efficient, transparent and predictable. A major initiative on conflict of interest in medical research, in association with Stanford University and Harvard Medical School, is well underway, with current plans for October 2002 forum and several white papers nearing completion. A new initiative brings together CMS, Harvard School of Public Health and CIMIT to examine better coordination between FDA marketing decisions and CMS coverage decisions. Finally, work with FDA, industry, and academic on the implementation of "least burdensome means" continues.

Key results during this period include:

- Boston-based conflict of interest forum organization. Following discussions with participants, planning preparation for this forum continues, including drafting of three CIMIT white papers. These neutral, scholarly pieces will examine existing controls governing conflict of interest, as well as the mandate to commercialize the results of federally funded research under the Bayh-Dole Act of 1980. The forum itself has been re-scheduled to October 2002, reflecting national developments beyond CIMIT's control.
- Coordination of FDA marketing and CMS coverage decisions. Initiated in January 2002, this on-going project brings together CMS, the Harvard School of Public Health and CIMIT to examine paradigms for better coordination of these related but disparate processes. A white paper authored by Stanley Wang, M.D., J.D., intern in Regulatory Affairs at CIMIT will be delivered to CMS' Director of Coverage and Analysis prior to the complete of the 2001-02 academic year.
- Assisting FDA in implementing the "least burdensome means" concept as required by the Food and Drug Administration Modernization Act of 1997 (FDAMA). The Regulatory Affairs Program continues to function as a point of access to FDA's Center for Device and Radiological Health, providing information and academic resources to FDA managers and line reviewers. During this quarter, details on a presentation of CIMIT's vulnerable plaque work were finalized with the agency.
- Regulatory tracking and education. The Program continues its publication of a well-received regulatory newsletter, which saw expanded distribution throughout the academic medical community and government. In addition, the Director of Regulatory Affairs delivered several invited presentations to the Harvard Medical School and CIMIT.

Specific Aim 1: Maintain an infrastructure for addressing systemic regulatory and coverage/reimbursement issues in device development; maintain adequate capacity to address product-specific questions, as well as educate the CIMIT community on regulatory issues.

Progress: Project completed.

Plan: To continue our efforts in Regulatory Affairs under Cooperative Agreement No. DAMD17-02-2-0006.

Specific Aim 2: Identify key “systemic” regulatory and coverage/reimbursement issues facing the device development process across product lines.

Progress: Project completed.

Plan: To continue our efforts in Regulatory Affairs under Cooperative Agreement No. DAMD17-02-2-0006.

Our dialogue with Harvard Medical School and Stanford University is directly applicable to the conflict of interest issue and will continue to guide Program efforts in this area. Discussions with CMS as part of the FDA/CMS coordination project will provide improved insight into government needs. Within CIMIT itself, discussions continue on where the Program may be direct its resources, with consideration being given to CIMIT’s bioterrorism initiative and the BodyLan advanced, modular sensor process.

Specific Aim 3: Develop and apply a process for developing workable solutions to regulatory and coverage/reimbursement issues.

Progress: Project completed.

Plan: To continue our efforts in Regulatory Affairs under Cooperative Agreement No. DAMD17-02-2-0006.

APPENDIX C. LIST OF CIMIT PROJECTS AND PRINCIPAL INVESTIGATORS

CIMIT RESEARCH PROJECTS

ENDOVASCULAR DEVICES

Cardiomyocyte Repopulation using Percutaneous Delivery of Tissue

Engineered Systems

Stephen Oesterle, MD MGH

MINIMALLY INVASIVE SURGERY

Minimally Invasive Cardiac Surgery – Endoscopic Coronary Anastomosis

David Torchiana, MD MGH

Endothelial Activation Markers as Molecular Targets for Innovative, Minimally Invasive Diagnosis and Therapy in Cardiovascular Disease

Michael Gimbrone, MD BWH

Develop a Computer-Based Three-Dimensional Imaging Treatment Planning System to Drive an Endoscopically Placed, Miniature, Facial Skeletal Distraction Device

Leonard B. Kaban, MD, DMD and Maria Troulis, MD, MGH

Operating Room of the Future

David Rattner, MD, MGH

Application of a Robotics Interface in Surgery

Robert Howe, PhD, HMA

IMAGE GUIDED THERAPY

MRI-guided Focused Ultrasound Treatment of Breast Cancer

Ferenc Jolesz, MD BWH

ALA Enhanced Fluorescence Imaging of Barrett's Epithelium

Norman Nishioka, MD MGH

OCT Imaging of Esophageal Lesions

Norman Nishioka, MD MGH

Segmentation of Bone From CT and Vessels From MRA Data

Carl-Fredrik Westin, PhD and Ron Kikinis, MD, BWH

Real-time Registration of Intra-operative Ultrasound with Pre-operative

CT/MR for Image Guided Therapy

Eric Grimson, PhD MIT

TISSUE ENGINEERING

Degradable Conductive Polymers

Robert Langer, ScD MIT

Polymer-based Gene Delivery Platform

Robert Langer, ScD MIT

Transdermal Drug Delivery and Chemical Sensing for Neonates Using Skin Electroporation

James Weaver, PhD MIT

Synthesize Vascularized Living Systems from the Platform of Two-Dimensional Silicon Microfabrication Technologies and Adapt to Three-Dimensional Living Devices

Joseph Vacanti, MD MGH

Synthesize Vascularized Living Systems from the Platform of Three-Dimensional Printing Technology

Joseph Vacanti, MD MGH and Jeffrey Borenstein, PhD, Draper Laboratory

Minimally Invasive Meniscal Repair with Tissue Engineered Cartilage

Thomas J. Gill, MD and David J. Zaleske, MD, MGH

Development of a Novel *in vivo* Recombinant Protein Delivery Device

Designed to Regress Abnormal Tissue: Recombinant Human Müllerian Inhibiting Substance (rhMIS) Producing Cells on Biodegradable Matrices

David MacLaughlin, PhD MGH

Determine the Role of Mesenchymal Stem Cells in Fetal Tissue Engineering

N. Scott Adzick, MD, University of Pennsylvania (UPenn) and Children's Hospital of Philadelphia (CHOP) and Alan W. Flake, MD, CHOP

SIMULATION

Design, Fabricate and Validate Procedural Medical Simulators

Steven L. Dawson, MD MGH

NEW INITIATIVES

Lung Volume Reduction Using a Bronchoscopic Approach

Edward Ingenito, MD BWH

Outcome Assessment in Menorrhagia

Johana L. Bosch, PhD GH

TRAUMA AND CRITICAL CARE

Microsensors – Real-Time Blood Assay

Christopher Dube, PhD Draper Laboratory

Application of Microwave Imaging to Rapid Non-Invasive

Detection of Intracranial Hematoma

Geoffrey Ling, MD, PhD Uniformed Services University of the Health Sciences, USUHS, Bethesda, MD

Near-Infrared Reflectance Spectroscopy (NIRS) to Assess Regional Ischemia both during Trauma Resuscitation and at the Bedside in the Intensive Care Unit

Juan Carlos Puyana, MD BWH

Noise-Enhanced Tactile Sensation for the Management of Sensory Deficits in Patients with Stroke

Casey Kerrigan, MD Spaulding Rehabilitation Hospital

VULNERABLE PLAQUE

Detection of Vulnerable Plaque using Optical Coherence Tomography

Brett Bouma, PhD MGH

STROKE

Acute Stroke Management – Neuro-Protection

Walter Koroshetz, MD MGH

MRI Guided Rapid Laser Endovascular Photoacoustic Recanalization (LEPAR) for Hyperacute Stroke and Stroke Predictive Modeling

R. Gilberto Gonzalez, MD, PhD MGH

Optical Monitoring and Imaging of Stroke

David Boas, PhD MGH

Neuronal Injury and Neuroprotection in Epilepsy: Proton Beam Radiation for Intractable Epilepsy

Jonathan Brisman, MD MGH

Telemedicine – Remote Stroke Videoconferencing Project

Lee Schwamm, MD MGH

APPENDIX D: LIST OF PERSONNEL RECEIVING PAY

PROGRAM/PROJECT TITLE	NAME	TITLE/ROLE
CARDIOVASCULAR		
Management	Muller, James, M.D.	Cardiovascular Program Team Leader
	Brady, Thomas, M.D.	Cardiovascular Program Team Leader
	Ryan, Jeanne	Administrative Assistant
OCT for plaque characterization	Bouma, Brett E., Ph.D.	Principal Investigator
	Jang, Ik-Kyung, M.D., Ph.D.	Investigator
	Brady, Thomas, M.D.	Investigator
	Shishkov, Milen, Ph.D.	Research Fellow
	Kang, Dong-Heon, M.D.	Investigator
	Yabushita, Hiaroshi, M.D.	Investigator
	Schlendorf, Kelly	Clinical Studies Coordinator
Minimally invasive cardiac surgery	Torchiana, David F., M.D.	Principal Investigator
	Howe, Rob, Ph.D.	
	White, Jennifer, M.D.	Research Fellow
	Titus, James	Lab Supervisor
CANCER		
Management	Tanabe, Kenneth, M.D.	Cancer Program Team Leader
NIR spectroscopy-Barrett's esophagus	Nishioka, Norman, M.D.	Principal Investigator
	Schomacker, Kevin, Ph.D.	Co-Investigator
	Brand, Stephan, M.D.	Research Fellow
	Puricelli, William, R.N.	Clinical Coordinator
OCT imaging of esophageal lesions	Nishio0ka, Norman, M.D.	Principal Investigator
	Bouma, Brett, Ph.D.	Co-Investigator
	Asimellis, George, Ph.D.	Research Fellow
	Puricelli, William, R.N.	Clinical Coordinator
MRA & CT Segmentation	Westin, Carol F., Ph.D.	Principal Investigator
STROKE		
Management	Koroshetz, Walter, M.D.	Stroke Program Team Leader
	Schwamm, Lee, M.D.	Stroke Program Team Leader
	Gonzalez, R., Gilberto, M.D., Ph.D.	Stroke Program Team Leader
	Lee, Albert, M.D.	Researcher
Stroke Metrics	Sorensen, Gregory, M.D.	Principal Investigator

PROGRAM/PROJECT TITLE	NAME	TITLE/ROLE
Tissue characteristic in human acute ischemic stroke	Sorensen, Alma Gregory, M.D.	Principal Investigator
Assessment neoroprotective brain cooling	Koroshetz, Walter, M.D.	Co-Investigator
	Lee, Albert, M.D.	Research Scientist
Laser thrombolysis of clot	Gonzalez, R. Gilberto, M.D., Ph.D.	Principal Investigator
Diffusion optical tomography brain hemorrhage	Boas, David, M.D.	Principal Investigator
	Koroshetz, Walter, M.D.	Co-Investigator
	O'Donnell, Joan, R.N.	Nurse Coordinator
	Gaudette, Thomas, Ph.D.	Engineer
	Marota, Joseph, M.D.	Medical Staff
	Mandeville, Joseph, M.D.	Medical Staff
Use proton beam rad – tract epilepsy	Brisman, Jonathan, L., M.D.	Principal Investigator
Measure CV reactivity-functional MRI	Greenberg, Steven, M.D., Ph.D.	Principal Investigator
	McKenzie, Sarah, B.A.	Research Assistant
TRAUMA		
Management	Puyana, Juan Carlos, M.D.	Trauma Program Team Leader
	Puyana, Juan Carlos, M.D.	Principal Investigator
NEW INITIATIVES	Dube, Christopher, Ph.D.	Principal Investigator
	Calderwood, Steven, M.D.	Principal Investigator
Management	Dawson, Steven, M.D.	New Initiatives Program Team Leader
	Brady, Thomas, M.D.	New Initiatives Program Team Leader
Computer-based distraction device	Kaban, Leonard B. D.M.D., M.D.	Principal Investigator
	Seldin, Edward B., D.M.D., M.D.	Principal Investigator
	Emanuel, David, D.D.S., M.D.	Investigator
ADV TECHNOLOGY TEAMS		
Management	Pien, Homer, Ph.D.	ATT Program Team Leader
	Dawson, Steven, M.D.	ATT Program Team Leader
Management	Vacanti, Joseph, M.D.	ATT Program Team Leader
	Kelly, Miranda	Administrative Assistant
	Oesterle, Steven, M.D.	ATT Program Team Leader
	Harvey, Susan	Administrative Assistant
Tissue Engineering	Vacanti, Joseph, M.D.	Principal Investigator

PROGRAM/PROJECT TITLE	NAME	TITLE/ROLE
	Langer, Robert, Sc.D.	Principal Investigator
	Anderson, Rox, M.D.	Investigator
	Borenstein, Jeffrey, Ph.D.	Principal Investigator
	Kaihara, Satoshi	Surgical Fellow
	Solan, Lalan	Research Technician
	Kohei Ogawa	Surgical Fellow
	Rahul Koka	Technician
	Cathryn Sundback	Post-Doc Fellow
	Mohammad-Reza Kaazempur-Mofrad	Post-Doc Fellow
	Jamie Lien	Student
	Michael Raven	Student
	Peter Linde	Surgical Fellow
	Michio Sato	Surgical Fellow
	Tracy Griksheit	Surgical Fellow
	Julie Fuchs	Surgical Fellow
	Terai Hidetomi	Surgical Fellow
CORE PROGRAMS	Rattner, David, M.D.	Principal Investigator
CIMIT Clinical Programs	Gesner, Charlotte	Administrative Assistant
CIMIT Education Program	Mezrich, Reuben, M.D., Ph.D.	Director
	Shaffer, David, Ph.D.	Director
	Weissbach, Karen	Program Specialist
	Sage, Melanie	Administrative Assistant
	Strod, Deborah	Technology Associate
Technology Assessment Program	Gazelle, Scott, G. Ph.D.	Principal Investigator
	McNaughton-Collins, Mary, M.D.	Outcomes Analyst
	Halpern, Elkan F., Ph.D.	Statistician
	Gleason, Suzanne, Ph.D.	Economist
	Lester, Jessica, M.D.	Research Associate
	McMahon, Pamela, B.S.	Research Associate
	Maddeford, Jennifer	Staff Assistant
CIMIT OTD	Rosen, Jonathan, Ph.D.	Director
CIMIT Strategy	Parrish, John A., M.D.	CIMIT Director
	Nolan, Marybeth	Administrative Assistant
	Shulman, Beth	Secretary
CIMIT Leadership	Brady, Thomas, M.D.	CIMIT Executive Director
	Muller, James, M.D.	CIMIT MGH Director
	Ryan, Jeanne	Administrative Assistant
	Vosburgh, Kirby, Ph.D.	Leadership

PROGRAM/PROJECT TITLE	NAME	TITLE/ROLE
	Deutsch, Thomas, Ph.D.	Science Recorder
	Anderson, Rox, M.D.	Leadership
	Jang, Ik-Kyung, M.D., Ph.D.	Leadership
	Nishioka, Norman, M.D.	CIMIT Awards Program Director
	Cohen, Melissa	Administrative Assistant
	Isaacson, Keith, M.D.	Leadership
	Stiller, Jane	Administrative Assistant
CIMIT Operations	Osborn, Lynne R.	Director of Administration and Finance
	Garber, Kelly	Administrative Assistant
	Herry-Galloway, Michelle	Administrative Assistant
	Robichaud, Annette	Finance Administrator
	Pagett, Jane	Financial Analyst
	Taylor, George	Courier
CIMIT IS	Cho, Unsuk	IS Manager
	Greaves, Kenneth	IS Manager
CIMIT Program Development	Kigin, Colleen	Director of Program Development
	Chandonnet, Grace	Staff Assistant II
	Palumbo, Andrea	Clinical Studies Coordinator
	Schlendorf, Kelly	Clinical Studies Coordinator
	McAuliffe, Daniel	Stoke Program Manager
	Stod, Deborah	Technology Associate
CIMIT Business Development	Crosby, Janice	Director of Industry Liaison Program
	Humphrey, Ann	Industry Account Manager
	Carpenter, Janine	Industry Project Coordinator
	Hanna, Lamees	Industry Program Coordinator
CIMIT FDA Program	Smith, John J., M.D., J.D.	FDA Program Director

APPENDIX H. GRADUATE DEGREES RESULTING FROM AWARD SUPPORT

No degrees were awarded this year.